

Planning Ahead for Public Research in Britain

THE third report of the Council for Scientific Policy which appeared two weeks ago (see *Nature*, 239, 481; 1972) marks a turning point of some importance in the administration of scientific research in Britain. Later this month, the council will be replaced by a new body called the Advisory Board for the Research Councils on which the research councils and several government departments will be represented as of right, and which will have as its principal task the supervision of arrangements which have been devised for implementing those of the Rothschild proposals which the government adopted in July.

It is only fair to say that the replacement of the Council for Scientific Policy by a body more formally linked with the machinery of government is not merely another of Lord Rothschild's little plots but is also in line with the recommendations of the Council for Scientific Policy itself. Sir Frederick Dainton's working group, whose report was published at the same time as Lord Rothschild's almost exactly a year ago, argued that the executive heads of the research councils should be members of the board and that government departments should be represented directly as well as through the Scientific Adviser to the Cabinet. The Dainton proposal would have given the new board a full-time chairman and executive charge of some parts of science policy at present the responsibility of the Department of Education and Science—international relations, for example. In the event, the government has settled for less than that. The chairman of the board will be a part-timer (none other than Sir Frederick Dainton himself) and the board's functions will be strictly advisory, as were those of the Council for Scientific Policy.

In the circumstances, there are several timely questions to be asked. Will the new board be able to meet the demands now likely to be made of it? Why in any case was the old council unsatisfactory? The council's third report is a useful starting point, for it includes a description of how the council has tried to play a part in the administration of publicly supported research in the eight years of its existence. Its central task has been to advise the Department of Education and Science on the allocation of resources between the research councils, and the report explains how individual councils were invited at the beginning of each year to submit an estimate of their financial needs in the five succeeding financial years. The council would then ask critical questions of the individual research councils and submit its recommendations to the Department of Education and Science in time for these to be incorporated into the government's annual forecast of public expenditure. One important scandal is that the government's own estimates of public expenditure on research and development have, in the past few years, been innocent of detailed advice from the Council for Scientific Policy so that "the council has restricted its advice to the parameters set by the white papers".

The report for the working group set up in 1970 to

develop criteria for the determination of priorities in research, included as an appendix in the CSP report, is a good example of how tentative the council has become. The working group says, quite clearly, that the need for criteria is especially important when the public funds available for science are likely to grow less quickly than in the past, and when indeed there is a prospect that, in real terms, the science budget will decline. It rejects the view that the government should make a general provision for non-applied research, letting the scientific community itself decide how the money should be spent, and, taking its text from Sir Brian Flowers, says that the problem is how best to balance the internal forces representing the natural development of science and the external forces representing the aims of society at large. There follows a perfectly innocuous list of the several criteria that might be adopted—internally, the report says, it is important to consider the intrinsic excellence of the work being supported, its pervasiveness, its cultural value and its relationship with research elsewhere. Among the council's external criteria are such considerations as economic benefit, social benefit and the usefulness of research projects as a means of training people and as contributions to national prestige. The council also emphasizes the need that any programme of publicly supported research should be fitted into a larger view of what resources are available, manpower as well as money. Nobody will quarrel with this exercise in classification and definition. Its weakness is that it has nothing to say about the machinery by means of which these criteria should be satisfied except the general implication that the research councils as they are and will become are well equipped to do the job.

The new Advisory Board for the Research Councils would be well advised to take a much sharper line. It is all very well for the CSP's working party on criteria to have decided that the research councils in their wisdom could collectively make arrangements for the support of fundamental research in universities and for the demands that will be made, in the years ahead, by government departments with research contracts to let, but this view overlooks the differences which are already apparent between the research councils and the need that some at least of the work that they sponsor should be insulated

Evolution Denied

The Editor of *Nature* has so far received two names of those who dissent from the accepted theory of evolution (see *Nature*, 239, 420; 1972). They are as follows: Dr Garret Vanderkooi, Assistant Professor of the Institute for Enzyme Research at the University of Wisconsin and Dr Harold Van Kley, Assistant Professor in the Department of Chemistry at Saint Louis University.



from the pressures likely to arise in the years ahead. At least three of the five research councils will be increasingly involved, in the years ahead, with contract work for government departments, but the Science Research Council, already distinguished from the others by the extent of its involvement in university research, is not to be required to make contracts for applied research in the next three years. So does it not follow that the Science Research Council could advantageously become the coordinator of central government support for research in the universities? One possibility, which should not be ignored simply because it is apparent that the research councils now need a prolonged period of consolidation, is that the Science Research Council should be given charge of all research council expenditure in universities. An immediate benefit would be that the Science Research Council could pursue its policies of selectivity and concentration more effectively if it were recognizably in charge of all the purse strings for public support of university research. In the long run, it would also be important if one of the research councils could set itself up as a custodian of the integrity of university research as a whole, for, whatever the government's present intention, it is likely and even desirable that there will be further attempts to make the research councils responsible for agriculture, medicine and the natural environment still more responsive to social needs. Nobody will deny that the bulk of what the government spends on scientific research should yield results of practical value but it is also important that academically directed research should also continue. To ask that the Science Research Council should become the sole sponsor for such activities is not to plead for ivory towerism or even to ask that the council should abandon its laudable encouragement of university courses and research projects which are closely linked with industry, but is merely to anticipate that in the very near future, there will be an urgent need that one of the research councils should be recognized as the custodian of the integrity of university research.

It is also important that the advisory board should be equipped to avoid the errors, most of them errors of omission, which made the old Council for Scientific Policy seem ineffectual even to its members. Eight years ago, the council was well placed to become an independent critic of the government's policy on research and development in all fields of government. The fact that the council was formally appointed so as to advise the Minister of Education need not have prevented it from speaking its mind on policies on defence research or on such questions as the organization of research and development in telecommunications, for example. In the event, the council seems to have stuck closely to its formal brief. Its successor, the Advisory Board on the Research Councils, will be even better placed to deal with a broad range of issues, if only because proper supervision of the customer-contractor relationship will allow it to decide not merely whether the research councils are carrying out their part of the customer-contractor bargain properly but also to consider whether the customers are asking the right questions. In short, the advisory board could, if it chose, become an influential source of commentary on the working of British science policy as a whole. It can, however, only do so if it is properly equipped with professional staff able to undertake the studies which need urgently to be carried out. The broodings on the economic benefits of basic

research which the Council for Scientific Policy commissioned at British universities (and which are described in the third report) are insufficiently sharp to serve as models for the work the new advisory board should undertake.

Grouse Grouse

THOSE who carry out research on grouse cannot help but be afflicted by the derision which attaches to those who shoot these unfortunate animals (*Lagopus lagopus*) in the hectic days which begin each summer on August 14. This no doubt is why the Nature Conservancy report on research in Scotland for 1968-70 (just published, HMSO, £0.50) includes a solemn justification of the research programme of the Grouse Research Group. The report says that the grouse and the ptarmigan (*Lagopus mutus*) are the commonest vertebrates in a large part of Britain and that, as a consequence, "it is important to know more about the ecosystem and how it may be managed". The report goes on to quote "the interest of its visitors—ecologists, shooting men and human biologists"—perhaps forgetting that visitors to the Cairngorms may often have other reasons, perhaps quite personal, for visiting the Cairngorms. It adds that a better understanding of the ecology of grouse and ptarmigan and of their techniques of population regulation, still rudimentary, may throw light on the population cycles of northern animals in quite a fundamental way, and that there may be practical benefits in tourism, recreation and "land use in Britain and other countries". Finally, the report says, a better understanding of the natural mechanism of population regulation in grouse and ptarmigan, species which are notoriously profligate in their requirements of space, may be important for human welfare because "intensive studies of spacing behaviour in animals are of increasing interest to social psychologists, psychiatrists, planners and others who are beginning to study the much neglected field of man's aggression and spacing problems in mental hospitals, housing flats and elsewhere".

In these enlightened days, nobody will wish to undermine an honest attempt to make interesting research useful as well. And no doubt the honest fellows who take to the grouse moors with bags of fertilizer and egg-collecting apparatus each season are as anxious as the rest of us that the problems of the cities they have left behind should be dealt with imaginatively and sympathetically. But do they seriously consider that research on grouse (and ptarmigan) is how one of Lord Rothschild's customers would specify a better understanding of daunting social problems? And if not, do they not consider that future reports on this enchanting subject for research should take a much more sober line?

Cancer Research

LORD ZUCKERMAN'S report on cancer research in the United Kingdom (see page 4), in passing a valuable review of the work now under way in British institutions, is a modest and even over-timid document. Its origins appear to be the Prime Minister's anxiety that President Nixon's great cancer programme should not go unremarked in Britain. (Perhaps Mr Heath was needlessly

alarmed: in the past few days—see page 8—the United States President has found it necessary to veto the Health, Education and Welfare Bill to which the cancer programme is attached.) What Lord Zuckerman says is that no purpose would be served by a sudden increase in funds for cancer research in Britain, because these could not be used effectively. He does, however, argue for “a steady and substantial increase over the years”, believing that the Coordinating Committee for Cancer Research has now efficiently embarked on the definition of goals in cancer research and that, in any case, it will in due course be necessary to provide a British counterpoise to the attraction for young researchers which the American programme will no doubt acquire in due course.

Unhappily there is at least the possibility that on this occasion Lord Zuckerman has been over-sanguine. Nobody will—or at least should—quarrel with his opinion that the sheer scale of the programme on which the Americans have embarked may—when the problem of “curing cancer” turns out to be less tractable than the publicists suppose—create yet another round of disillusionment. It is also self-evident that no purpose will be served by pouring British money into enterprises for the screening of chemotherapeutic drugs, a job well done by American institutions, public and private alike. It is also reasonable to argue, as Lord Zuckerman does, that there is scope for more epidemiology, for more public education, for improvements of the hospital services on the therapeutic side (and for operational research to decide how best to deliver cancer treatment to those in need of it) as well as for the sympathetic evaluation of the methods by which terminal illness is at present dealt with in British hospitals. All this is good, but Lord Zuckerman seems entirely to have overlooked one of the most serious anomalies in the present pattern of cancer research in Britain—of the £10 million a year at present spent on basic research in cancer, no less than 60 per cent is at present raised by means of voluntary societies, principally the Imperial Cancer Research Fund and the Cancer Research Campaign. One practical consequence is that the pattern of the research at present undertaken is more arbitrary than if it had been entirely supported by public funds (and it will be some time before the coordinating committee is able to exert an entirely rational influence). Another is that the system as a whole has to carry more structural inefficiency than is desirable. And there is always the danger that contributions to the voluntary societies which at present spend the lion's share on cancer research will fluctuate not merely with the prosperity of the country as a whole but with the changing public view of the hopefulness of these activities.

Lord Zuckerman could have said more. To the extent that one of the continuing conundrums in cancer research is the recognition that the first need is a better understanding of the processes by means of which normal cells beget other normal cells, quite fundamental cell biology can also properly be regarded as cancer research. By this test, of course, the public contribution to cancer research through agencies such as the Medical Research Council is much larger than appears at first sight. But does it not follow that somebody should ask whether enough is being done in molecular biology and cellular immunology to satisfy the needs that may be felt ten years from now? And is it too soon for potential customers to begin to formulate the questions which in due course they will have

to ask of contractors in the field, university departments, the units of the Medical Research Council and the like? That is one question that Lord Zuckerman has overlooked. Another is the method by means of which a country such as Britain should seek to keep in touch with what is happening elsewhere. Lord Zuckerman's outwardly impressive list of institutions in the United States and elsewhere with which British laboratories at present collaborate is more than a little misleading, for many of the institutional links which he describes depend on the chance acquaintance of individual researchers. Might it not have been sensible to advocate that if the United States Congress is determined to spend \$1,000 million on cancer research in the next few years, the British government should spend a tiny fraction of that sum on a programme of collaboration to enable a handful of people from Britain to work each year in American laboratories, and to support the kinds of exchanges between working scientists which are, in the last resort, the most efficient means of information retrieval? But collaboration with mainland Europe on this and other enterprises is also necessary.

100 Years Ago



RESEARCHES IN GREENLAND*

In Umenak Fiord I ascended a mountain of about 7,000 ft. with five Greenlanders, and took my theodolite to the top. As you know the weight of the instrument, you will be partly able to appreciate this performance. The ascent, first over swamp, then over basalt *débris* which reposed insecurely upon solid basalt, and finally, at the top, up columnar basalt, was a sweet thing of its kind. The picture of your humble servant being lowered by a rope, dangling like a bundle from a crane, will, perhaps, to some people, be more interesting than the results obtained by the theodolite. These, however, were not unimportant. My peak, an isolated one, commanded a view of almost the whole of the Umenak district (which contains the highest mountains of Greenland proper), and a magnificent view of the “inland-ice.” I found the general elevation of the mountains exceeded by about 2,000 ft. the height previously assigned to them. Of the altitude of the “inland ice” I shall write on a subsequent occasion.

A large part of my time in the Waigat was occupied by the measurement of a base line. This was the most important piece of work that I undertook, and it was successfully executed. I find the Waigat to have in some places scarcely half the width which our maps give it. I find its mountains to be about double the altitude that they have been supposed to be; and Hare Island I find to be twice the length represented upon the Admiralty Chart; Hare Island has some points of particular interest. I got from it a rather large collection of fossil plants, and went to its top (1,800 ft.). From the summit, at midnight, I distinctly recognised the mountain called Sanderson's Hope, near Upernavik, which was distant from me 140 miles!

EDWARD WHYMPER

Written on board the brig Hvalfisken as it proceeded out of the harbour of Godhavn, Sept. 10, 1872.

From Nature, 7, 8, November 7, 1872.

OLD WORLD

Conference Meets on Dumping of Waste at Sea

THE inter-governmental conference on the dumping of waste at sea got under way in London this week with hopes high for its success. By the end of the ten-day meeting, a convention should have been signed prohibiting the dumping of certain wastes and limiting the dumping of others.

Mr Peter Walker, Secretary of State for the Environment, who opened the conference, said last week that he saw no reason why agreement should not be reached. There is, he said, no reason to delay this convention which, if it is agreed, will be the first tangible fruit of Stockholm. Mr Walker pointed out that Britain has already agreed a local convention on dumping in the North Sea and North Atlantic with other states that border those waters, and he hoped that a global convention would emerge from the current conference. Seventy-five countries are represented at the meeting, with eight more attending as observers along with representatives from eight United Nations agencies.

The idea is that a general convention will be drawn up, forbidding the disposal of certain wastes including organochlorines, heavy metals, persistent oil and tar wastes and bulky objects likely to endanger vessels. This global agreement will then be supplemented by a series of local agreements which will take into account local conditions. The Oslo Convention (as the North Sea agreement is known) is one example, and the Italians are already setting up a similar agreement to cover the western Mediterranean. In his opening speech, Mr Walker argued that once really toxic wastes have been eliminated from the seas, other wastes can be disposed of safely in varying quantities depending on the area. "For example we could safely dump in Liverpool Bay four or five times as much sewage sludge as goes there now . . . on the condition that the sludge does not contain more dangerous contaminants than we can help."

Mr Walker also said that the approach to waste disposal must be a total one. "If we do not put waste into the sea, it has to go somewhere else. It would be silly to put it in a hole in the ground if that contaminated water supply". Nations therefore need to help each other with their waste disposal problems and share expertise in destroying noxious wastes.

Mr Walker made it equally plain that once a global ocean-dumping convention is agreed, the British Government is eager to see a convention on river

pollution drawn up, and more work needs to be done on pollution from shipping.

The conference is a conference of officials rather than of ministers, with Britain's delegation including representatives from the Department of the Environment, the Ministry of Agriculture Fisheries and Food, the Foreign Office and the Department of Trade and Industry. Dr Martin Holdgate, head of the DOE's environmental pollution unit has been elected chairman of the conference.

One of the areas it is hoped the conference will cover is enforcement of the hoped-for convention. Mr Walker has made it plain that he hopes the convention will consist of more than pious promises and that methods of detection and enforcement will be agreed. Better methods for tracing culprits must be developed he said last week, and he referred to work on placing chemical tracing elements in tanker oil which would make it possible to trace dumped

oil to the tanker that carried it.

Mr Walker also pointed out that the conference is only one step in solving the problems of keeping the oceans clean. The International Marine Consultative Organization's 1973 conference on shipping matters will be another step, and the UN conference on the Law of the Sea, which is also planned for next year, will also help. "We cannot attain perfection in one great leap," he said, "We have to make progress as and when we can and there will be many steps on the road".

For the British Government, the London conference is a minor diplomatic coup. Mr Walker and Mr Maguire made a mark at Stockholm by their protestations that they could not wait for the setting up of a United Nations agency to sign an anti-dumping convention. At the time, they seemed to ride rough-shod over the feelings of maritime nations—Brazil, for example—not invited to the preparatory conference at Reykjavik.

RESEARCH

More Money for Cancer

A SUDDEN increase in funds for cancer research could not be used effectively according to Lord Zuckerman in a report on cancer research prepared at the Prime Minister's request. But "a steady and substantial increase over the years would probably yield valuable results".

Lord Zuckerman's report was prepared following President Nixon's huge increase in funding cancer research in the United States. But Zuckerman concludes that attempting to compete with the resources available in the United States—which will spend about \$440 million in the fiscal year 1972-3—would be wasteful, but he does recommend that accommodation for research be improved and that major laboratories be given the assurance of long-term support so that a career structure in cancer research can be established. Further, defence establishments that are being run down—such as the Microbiological Research Establishment, Porton—should be turned over to cancer research and international cooperation should be strengthened.

Lord Zuckerman states that he is worried about the links between research and the clinicians which are not as close as they might be, with the result that, through ignorance, the latest treat-

ments are not always applied. He also believes that money spent helping the families of those dying of cancer would be money well spent.

The planning of new research, Lord Zuckerman says, should be governed by three considerations. First, it must be realized that the basic branches of biomedical research are interdependent; the development of any one branch at the expense of the others would result in a loss of efficiency. Second, money alone will not buy new ideas; the research must be of sufficiently high scientific standard to be of value. Third, scientific talent of the quality necessary to deal with the exceptionally difficult problems associated with cancer research is in short supply; full training programmes and the provision of career prospects are needed.

The reaction of the two chief cancer research organizations—the Imperial Cancer Research Fund and the Cancer Research Campaign—to the report is favourable. The two charities between them will spend £6 million of the £10 million spent on cancer research this year in Britain. Both described the report as "very sensible", but emphasized that while a sudden massive injection of money would only create a shortage of adequate research staff, the "steady and substantial increase" which Lord Zuckerman prescribes is still vitally important.

RESEARCH AND DEVELOPMENT

Chief Scientist at MAFF

DR H. C. PEREIRA, Director of East Malling Research Station, has been appointed Chief Scientist to the Ministry of Agriculture, Fisheries and Food. His appointment completes the triumvirate at the head of the ministry's chief scientist organization which is to run MAFF's research and handle the programmes that the Agricultural Research Council will hand over to the ministry in April 1973. Mr W. F. Raymond and Dr G. A. H. Elton have already been appointed as Dr Pereira's deputies (see *Nature*, **239**, 300; 1972).

According to the ministry, Dr Pereira will be responsible both for providing the department with scientific advice on all its policies and for "framing, commissioning, and reviewing the ministry's research and development programmes", which will be considerably more extensive following the government's recent white paper on research and development which ruled that £5 million should be transferred this year from the ARC's budget to the ministry's; by 1975, £10 million a year will have been transferred.

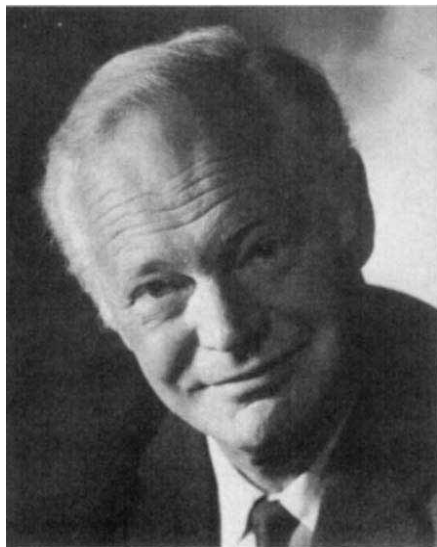
Dr Pereira, who is 59, has been Director of the East Malling Research Station since 1969, and is a member of the Natural Environment Research Council. Educated at the University of London, he worked at Rothamsted Experimental Station before moving to Africa where he worked in Kenya, Tanzania, Uganda, Rhodesia and Nyasaland, becoming founder director of what is now the Agricultural Research Council of Central Africa. He was elected a Fellow of the Royal Society in 1969.

Dr Pereira will be succeeded as Director at East Malling by Dr A. F. Posnette, currently the station's deputy director and head of its plant pathology section. Dr Posnette, who is 58, is a



Dr H. C. Pereira.

graduate of the University of Cambridge and also spent some years in Africa. He moved to East Malling in 1949, and has been its deputy director since 1969. He became a Fellow of the Royal Society in 1971.



Dr. A. F. Posnette

MEDICINE

Clean Bill for the Pill

THERE is no evidence to date that the contraceptive pill is carcinogenic. Following studies that lasted up to two years on 13,000 rats and mice, the Committee on the Safety of Medicines concluded last week that the evidence resulting from prolonged administration of both oestrogen and progestogen "cannot be interpreted as constituting a carcinogenic hazard to women when these preparations are used as oral contraceptives".

The committee's report discounts previous suggestions that the pill may cause liver damage and concludes "that no persistent disturbance of liver function occurs in women from the prolonged use of oral contraceptives".

The tests were run on mice for 80 weeks and on rats for two years, with three dose levels administered, equivalent to 2 to 5 times the human contraceptive dose, 50 to 150 times and 200 to 400 times. The only evidence for increased incidence of breast tumours came from the high dose administered over a large part of the animals' life span, and then the incidence was largely related to oestrogen. Progestogen is the dominant element in current oral contraceptives.

The committee recommends, however, that careful monitoring of women using oral contraceptives should continue, and says that it will consider the evidence of current American studies on primates and beagle bitches as and when it becomes available.

METEOROLOGY

Global Collaboration

from a Correspondent

THE first global weather experiment will be held in 1977. At a conference in Geneva last month the forty-one members of GARP, the Global Atmospheric Research Programme, agreed on the date for the first global experiment which will attempt to define the physical state of the atmosphere up to a height of 30 kilometres, and test mathematical models of the world's atmospheric circulation, in order to improve weather forecasting worldwide.

The conference agreed that its first task is to establish the best possible observing system for the experiment which is due to last for a year. Conventional observing networks will be improved, but extra coverage will be provided by nine geostationary and polar orbiting satellites that will be in orbit in 1977. The conference finally settled on 1977 because the USA and the Soviet Union are both planning by then to have two satellites in polar orbit equipped with cloud-imaging devices and sounding equipment for obtaining vertical temperature profiles.

Continuous pictures of cloud cover and information on winds from cloud displacements should be provided by two further satellites from the United States, and one each from ESRO, Japan and the Soviet Union. The only conspicuous gap that remains in the observing system is the information on winds in the tropics and on pressures at reference level in the southern hemisphere. Constant level balloons and ocean buoys may provide the solution.

The first global experiment will follow hard on the heels of the tropical experiment in 1974 (see *Nature*, **233**, 382; 1972) which will explore the primary energy source for the world's atmospheric circulation, knowledge of which, when tied in with the results of the 1977 programme, should provide a much better basis for understanding the world's circulation and predicting its behaviour.

The conference also agreed that a detailed study of the relationship between the atmosphere and ocean's currents and temperatures is needed.

The British contribution to the first global experiment, or FGGE as it has become known, will be to provide radiometers to sound mesospheric and stratospheric temperatures, to build three upper-air sounding stations at Mahe in the Seychelles, and Tawara and Funafuti in the south-west Pacific, and to prepare worldwide analyses and data sets for stratospheric levels based on the data received from the satellites.

NEW WORLD

Senator Kennedy Strengthens His Influence

by our Washington Correspondent

DURING the past four years, Senator Edward M. Kennedy has been quietly amassing considerable influence over science policy in the United States, or at least that part of it which is formulated by Congress. Nearly every item of legislation concerned with science that came before the 92nd Congress, for example, bore his stamp in some form, either because he sponsored or cosponsored it or because it was referred to one of the two subcommittees of which he is chairman. To be sure, he has burned his fingers badly on some bills and failed to get others into law, but without question Kennedy has emerged as the chief advocate for science on Capitol Hill—a position vacated by Emilio Q. Daddario in 1970 when he left Congress to make an unsuccessful bid for the governorship of Connecticut.

Last month, Kennedy's influence over congressional science affairs was increased even further, for he was appointed to the board of the Office of Technology Assessment, and will almost certainly become its first chairman when the board meets in January. Kennedy's chairmanship of the board is prescribed by the fact that the legislation establishing the OTA requires that the first chairman must be a senator, and Kennedy is the highest ranking among the Senate Democratic appointees. (The other members are Senators Ernest F. Hollings, Hubert H. Humphrey, Gordon Allott, Peter H. Dominick and Richard S. Schweiker, and Representatives John W. Davis, Earle Cabell, Mike McCormack, Charles A. Mosher, Charles S. Gubser and James Harvey.)

The chairmanship of the board will give Kennedy many more levers to pull, for all significant items of legislation involving science and technology will be referred to the OTA. Moreover, the board also has the power to initiate studies on its own—an authority which in theory should give a powerful chairman a means of obtaining critical analyses of virtually any scientific issue. The board also has the authority to appoint the director of the OTA and its Advisory Council—appointments which will profoundly affect the workings of the office long after the board has worked out its term. Finally, the first two years of operation of the OTA will in many respects be its most critical, simply because it will be finding its own way. In such a situation, a powerful chairman of the board can put his stamp on policy.

Kennedy's appointment to the board of the OTA is only the latest in a series of appointments which have gradually given him an expanding influence over scientific affairs. The first influential appointment came in 1968, when Kennedy was given the chairmanship of the *ad hoc* subcommittee of the Senate Committee on Labor and Public Welfare set up to examine amendments to the National Science Foundation Act. The amendments, which were in fact sponsored by Kennedy and Daddario, provided for annual authorization hearings to be held by Congress, and in the 90th Congress a permanent subcommittee was set up to oversee the workings of the NSF. Kennedy was given the chairmanship of that committee.

His next scientific power-lever came two years later, when he became chairman of the Health Subcommittee of the Senate Committee on Labor and Public Welfare, following the departure from

Congress of Ralph Yarborough, who lost a Texas primary election. Although the subcommittee has been chiefly concerned with questions of health care delivery, the chairmanship has given Kennedy a strong voice on cancer legislation and other bills concerned with biomedical research.

Has Kennedy been successful in wielding his power over scientific affairs in the 92nd Congress? The answer is yes and no. For one thing, the two chief items of scientific legislation which he sponsored turned out to be less than completely successful. The first was the bill designed to set up a NASA-style agency devoted to finding a cure for cancer, because of which Kennedy incurred the wrath of much of the biomedical community. Kennedy's original plan came to grief after it was passed by the Senate because of the weight of public opinion in favour of keeping cancer research within the National Institutes of Health. His posi-

SCIENTIFIC EXCHANGES

More Cracks in the Ice

by our Washington Correspondent

A GROUP of scientists from the Peoples' Republic of China will visit the United States at the end of November, hard on the heels of a party of medical doctors which has just completed a three-week tour of hospitals and medical research institutions. The two groups are the first official visitors to the United States from the Peoples' Republic (apart from the famous table tennis team) since the cold war of the early 1950s, and American scientists are hoping that the two visits will mark the beginning of a fruitful series of exchanges between the two countries.

Although both groups are official guests of the National Academy of Sciences, much of the credit for their visits must go to the Federation of American Scientists, a small but intellectually influential organization of scientists, which lobbies on Capitol Hill for liberal causes such as arms control. The federation's independence from the federal government made it the primary channel for communication with the Chinese Academy of Sciences when the diplomatic ice between the United States and the People's Republic began to crack last year.

A great deal of the spadework for the visit of the Chinese scientists later this month was in fact completed during visits to China by delegations

from the FAS in May and September this year. The visiting Americans then found Chinese scientists uncertain whether the academy is an official organization of the federal government and also concerned about the academy's ties with Taiwan. These fears have evidently been resolved, for the mission of the Peoples' Republic of China to the United Nations last month relayed a joint message to the academy and the federation accepting invitations from both organizations to the Chinese Academy of Sciences.

The federation and the academy agreed that the academy should play host to the Chinese visitors because of its experience in dealing with visiting groups of scientists and also because of its larger resources. Dr Jeremy J. Stone, director of the FAS, said last week that he is "happy with the way it has worked out" and that he believes the federation has fulfilled the aims of its charter "to strengthen the international cooperation traditional among scientists and to extend its spirit to a wider field".

The group of Chinese scientists will visit the United States on November 23, after visiting the United Kingdom, Sweden and Canada. It will consist of Pei Shih-chang, biophysicist; Pai Chieh-fu, science administrator; Chang Wen-yu, high energy physicist; Chen Wei-chang, specialist in mechanics; Chien Jen-yuan, polymer chemist; Hu Shih-chuan, biochemist; and Li Fu-sheng, computer technologist.

tion was also not helped by the Administration, which backed the plan during its passage through the Senate, but dropped it like a hot potato when it became clear that it would be rejected by the House of Representatives.

Kennedy's other major piece of scientific legislation, the National Science Policy and Priorities Act, was successfully steered through the Senate, but failed in the House of Representatives. The bill would have increased federal expenditures on civilian research and development, given the National Science Foundation a greatly increased stake in science policy planning, set up conversion schemes for jobless scientists and given Kennedy even more influence over science policy, for the workings of the act would have come under the purview of his NSF subcommittee. The bill did, however, raise considerable debate and it will almost certainly be reintroduced next year.

In his other activities, however, Kennedy has been more successful. He has, for example, steered the bill launching a crusade against diseases of the heart, lungs and blood vessels through Congress. Similarly, he has helped to increase federal funding for programmes designed to attack sickle cell anaemia and has been instrumental in steering through the Senate the bill setting up the Office of Drug Abuse Prevention. His sponsorship of the bill establishing the Office of Technology Assessment is also believed to have been a vital factor in getting the bill rushed through Congress in the nick of time.

As for next year, Kennedy's chief preoccupation, apart from getting the OTA moving, will be with the Science Policy Act. It will be interesting to watch the possible manoeuvrings between the Nixon Administration—if it is re-elected—and Senator Kennedy, who is likely to be a Presidential candidate in 1976. The love-hate relationship over the cancer bill could be a taste of things to come.

TELECOMMUNICATIONS

US First for Canada

by our Washington Correspondent

THERE is more than a touch of irony attached to the planned launching next week of the first satellite developed solely for domestic communications. The satellite, named Anik (Eskimo for brother), was developed for the Canadian government by a United States corporation and will be launched from Cape Kennedy by an American rocket. Yet the United States will not get its own communications satellite into orbit until 1974 at the earliest. Regulatory tangles and dithering by the federal government have meant that United

States expertise has had to be exported before it is put to use at home.

Irony apart, however, the launch will be a landmark in communications history, for although it is seven years since Early Bird built a telecommunications bridge across the Atlantic, the Canadian government is the first to use telecommunications technology for domestic television broadcasting and telephone links. The launch, which is taking place on schedule, is also a vindication of the Canadian government's decision to give the chief development contract to the Hughes Aircraft Corporation of California rather than to Canadian companies.

Since Canada is a large and relatively sparsely populated country, it is, like the United States, a natural candidate for a communications satellite system. Anik will be able to accommodate up to ten colour television channels or 9,600 telephone links, and it will be followed by a similar satellite in about six months. Each satellite is planned to last for between five and seven years, and will provide television reception for the first time in remote areas from the Alaskan border in the north-west to Newfoundland in the east.

The two principal stations for transmission and reception are in British Columbia and near Toronto in Ontario. In addition, two northern stations will be capable of transmitting and receiving messages and television signals from Anik, six network television stations spread across Canada from Newfoundland to Saskatchewan will receive and transmit television signals and twenty-five television receivers will serve remote locations in Canada.

Developed by Hughes Aircraft for Telesat Canada, a self-supporting corporation formed by the Canadian government in 1969, Anik will be launched by a Delta rocket, probably on November 9. It will be placed in a highly elliptical orbit ranging from 196 to 62,301 km, and after checkout a rocket aboard the satellite will circularize the orbit at a synchronous altitude of 36,800 km above the equator. The launch will represent the first use of the so-called Delta "straight eight" rocket. Unlike the previous 91 Delta launchers, which were tapered at the join of the first and second stages, the rocket used to launch Anik will have a diameter of eight feet for all three stages. The rocket will also be the first Delta augmented by nine solid fuel strap-on rockets.

Two years ago, when the Canadian government announced its decision to give the \$30 million chief contract for Anik to Hughes, it was greeted with howls of protest and charges that such a move would sound the death knell for the Canadian space industry. But last month Robert Stanbury, Minister

of Communications in the Canadian government, pointed out that Canada would not have had its satellite either as cheaply or as quickly if it had been developed by Canadian companies. In any case, two Canadian companies were awarded subcontracts on the Anik satellite, and Hughes has recently awarded both of them subcontracts on another satellite. The Canadian government is also cooperating with NASA on the development of a second-generation experimental communications satellite—the CTS—which will pioneer use of the 12 GHz band. CTS is scheduled for launch in 1975, but it may not be ready until 1976.

Meanwhile, south of the border, the Federal Communications Commission is still ploughing through the proposals it has received in response to its belated decision to allow the development of domestic US communications satellite systems (see *Nature*, 238, 8; 1972). In any case, 18 to 24 months will elapse between the FCC's approval of a project and the launching of a satellite. The United States will thus get its own domestic telecommunications satellites some two years after it has launched them for Canada.

CEO

Two New Faces

by our Washington Correspondent

PRESIDENT NIXON has nominated two people to fill vacant posts on the Council for Environmental Quality. They are Dr Beatrice E. Willard, an ecologist from Boulder, Colorado, and John A. Busterud, at present Deputy Assistant Secretary of Defense for Environmental Quality. They will fill the positions on the three-member council that have been vacated by Dr Gordon J. F. MacDonald and Robert Cahn, who both resigned last month to return to private life.

Dr Willard was Assistant Professor of Biology at South Oregon College from 1963–64, and became Executive Director of the Thorne Ecological Institute of Boulder in 1965. She is now president of the institute. Among her society affiliations are membership of the Sierra Club, membership of the board of trustees of the Colorado chapter of the Nature Conservancy and membership of the Wilderness Society. Mr Busterud is a lawyer, specializing in conservation and anti-trust law. Before joining the Department of Defense in 1971, he was active in a number of conservation organizations in the San Francisco area.

AGRICULTURAL RESEARCH

Land Grants Covetted

by our Washington Correspondent

A LAW suit with important implications for many colleges and universities throughout the United States has now been filed in the US Court for the District of Columbia. The suit charges the Secretary of Agriculture and the Secretary of Health, Education and Welfare with misapplying agricultural research funds which go to land grant colleges and universities. The allegation is that the funds have been used chiefly for research which benefits large corporations and harms small farmers, farm workers and consumers—the very people who are supposed to benefit from the land grant institutions. The suit asks for all such research money to be withheld until guidelines are drawn up to ensure that the entire rural community will benefit from it. And, for good measure, it is alleged that the land grant programmes have been operated in violation of the Civil Rights Act.

The land grant colleges and universities were set up by an act of Congress in 1862 and they are funded jointly by the federal government, the states and private sources. The research institutions associated with them are, according to an amendment passed by Congress in 1955, designed to "promote the efficient production, marketing, distribution and utilization of the products of the farm as essential to the health and welfare of our peoples and to promote a sound and prosperous agriculture and rural life as indispensable to the maintenance of maximum employment and national prosperity and security". The suit suggests that Congress therefore intends the research conducted at land grant institutions to benefit "consumers, owner-operated family farms, the rural home and rural life".

But, according to the Migrant Legal Action Program Inc. and several other farm workers' and consumer organizations who have brought the suit, the bulk of the research supported by the land grant funds goes towards development of mechanization, pesticides and other programmes which chiefly benefit agricultural industry and which contribute to the growing unemployment in rural areas. The suit singles out the development of tomato harvesters and tobacco harvesters as two projects carried out by universities and colleges with land grant money which have led to much unemployment.

A central complaint about this research is that in spite of the large investment in research designed to mechanize farm production, land grant institutions have not been willing to spend money on research into the

effects of labour-saving devices on the rural population, and that other research programmes that may benefit small farmers are also being ignored. The suit therefore asks that guidelines be drawn up to ensure that "an equal amount of funds appropriated be spent on human, job training and job placement are spent on developing labor-saving devices, mechanization or pesticides whose express or resultant purpose is to replace labor". To help draw up such guidelines, the suit asks for an advisory committee to be established, with majority representation by consumers, small farm owners, farm-workers and others who are alleged to have been shortchanged by the land grant programme in the past.

As for consumers, the suit charges that land grant money has been used to develop such commodities as DES, coatings on fruit and vegetables to make them look more appetizing and devices for ripening produce after it has been harvested which are of dubious value in increasing the nutritional content of the produce. The plaintiffs therefore also suggest that consumers have missed their benefits from land grant institutions.

If successful, the suit would have a major impact on agricultural research in the United States, for according to the plaintiffs, in 1970 some \$306 million in federal, state and private funds was spent on research at land grant institutions. Clearly, the land grant research programme, according to the suit, "represents the public's primary investment of intellectual and scientific resources in rural America". The law suit is also another graphic example of the fact that the courts are increasingly having to settle broad social issues in the United States.

NIH

Nixon Wields the Axe

FOR the second time this year, President Nixon has vetoed the appropriations bill for the Departments of Labor and Health, Education and Welfare. This means that the National Institutes of Health must be content, at least until February next year, with the same level of funding that they received in the 1972 fiscal year (which ended on July 1). Ironically, many projects that have been touted by the Administration during the election campaign—the crusades against cancer and diseases of the heart, lungs and blood vessels, for example—will be hampered because of lack of money.

Nixon vetoed the bill because it would have entailed some \$530 million more than he had requested, and it is a casualty of his election-year promise to hold down taxes. He had already vetoed an earlier version of the Labor-HEW ap-

propriations bill which budgeted some \$1,800 million more than he asked for, but Congress sent him back the scaled-down version in the hope that Nixon would find it more palatable. There is also no chance that Congress can override the veto because it came after Congress adjourned.

Because Congress had already passed a bill which allows federal departments and agencies whose budgets have not been settled to receive the same amount of money that they were budgeted last year, the research institutes of the National Institutes of Health must be content with \$1,476 million instead of the \$1,580 million that the Administration had wanted to give them, or the \$1,700 million that the vetoed bill contained. They will continue to be funded at last year's level until Congress passes a new appropriations bill which is signed by the President—it is unlikely that such a bill will be ready before February, after the 1974 budget request has been sent to Congress. Hardest hit will be the National Cancer Institute which will have to wait for the \$90 million budget increase that the Administration had earmarked for it, and the National Heart and Lung Institute which would have had an increase of some \$22 million.

Short Notes**Slimming at New York University**

Faced with a huge financial deficit, New York University, a private university with more than 40,000 students, has been forced to lay off or retire 217 members of its faculty. Hardest hit is the School of Engineering and Science, which will lose more than 100 of its staff members. The moves have come after New York University last year ended up with a deficit of \$14 million, chiefly because of declining enrolments, cutbacks in government support and rising costs. James Hester, the university's president, hopes that the staff cutbacks (which amount to about 8 per cent of the total staff), combined with other austerity measures such as dropping minority courses like Italian, will halve the deficit by the next academic year, and remove it entirely by the 1974-75 academic year.

Kennedy Bill

Hearings on Senator Edward M. Kennedy's National Science Policy and Priorities Act are set to take place before John Davis's Subcommittee on Science, Research and Development this week. It is now unlikely that the committee will get the bill to the floor of the House in time for it to be passed before the election, and the committee is therefore expected to issue a report saying that the bill has merit but needs more study.

NEWS AND VIEWS

Prehistoric Man in Australia

ALTHOUGH an exaggerated Pleistocene antiquity for man in Australia was reported in *Nature* (153, 211) as long ago as 1944, a late Pleistocene age has been authenticated only within the past decade. The important discoveries made in the long, curving sand dune (lunette) named The Walls of China are a landmark in Australian prehistoric research, and their implications for human prehistory extend far beyond the confines of the sixth continent.

This semi-arid plain once contained a series of lakes (the Willandra system), which have been dry for some 15,000 years but whose waters were exploited by the Aborigines more than 30,000 years ago. The potential of the region was realized by J. M. Bowler, a geomorphologist, whose initiative prompted much of the collaborative effort reported on pages 46 and 48 of this issue of *Nature*. Bowler has assembled data crucial for the reconstruction of the Pleistocene climates of south-eastern Australia, but his evidence also has more widespread Quaternary application. The deep sedimentary record is easier to interpret than many of the classic glacial research areas and offers a wide range of possibilities for investigation. One of the byproducts was Barbetti's geomagnetic research, details of which were reported recently in *Nature* (239, 327; 1972). In few projects have dating problems been tackled from so many angles. To possess comparative radiocarbon dates from samples of charcoal, shell, apatite, collagen and soil carbonate, indicates both good fortune and an experimental approach to the problem.

Yet these more benign research features of the landscape were hidden from Russell Drysdale, artist of the harsh outback, whose painting "The Walls of China" in the 1940s symbolized this region for many Australians. Drysdale found a country stricken by drought, and his vision is of a melancholy landscape, riven by erosion and studded with contorted remnants of dunes and grotesque tree stumps blasted by sand. Drought and desolation still predominate, but the denudation of the lunette has provided a geomorphic and archaeological bonus, which has helped along purposeful interdisciplinary studies.

As the radiocarbon dates demonstrate, human occupation predates 30,000 years ago. During the past decade several excavations scattered over the continent have yielded dates earlier than 20,000 years, but this series is the firmest evidence of an age greater than 25,000 years. The best of the other claimants is Keilor, which has been investigated by Gallus. The secure dating of the Willandra evidence, and its complexity, adds considerably, however, to its significance.

Allen's archaeological survey established that the Aborigines exploited a wide range of terrestrial and lacustrine faunas, and even at the earliest sites they seem to have been so well adapted to the resources that Allen infers that they were not newcomers to the region. On the other hand, much of the Australian interior was, presumably, comparable, so trial and error experience during the process of land occupation may have preadapted the first settlers. One of the most interesting consequences of this adaptation was the accumulation, at site

5, of an extensive shell midden about 25,000 years ago. Middens once were "type fossils" of the Mesolithic; their occurrence is still rare on Palaeolithic sites in the Old World and rarer still in freshwater situations.

It is significant that in spite of a systematic survey of the region by both Bowler and Allen, all recorded faunal remains on these ancient sites of occupation are of modern species. The project has failed to contribute positively to the debate about the date and causes of the extinction of Australia's giant marsupial fauna, and those who claim that man and his fires were determining factors in the great extermination may argue that this implies the arrival of the first colonists at an even earlier date at sites which are as yet undiscovered. The absence of giant fauna also contrasts with earlier discoveries at Lake Menindee lunette, a similar environmental setting, where eroded extinct marsupial bones and artefacts were believed to be associated and to date from the time interval between 18,000 and 26,000 years ago. It is possible that the Menindee stratigraphy was more complex and that the site merits further investigation. Recent discoveries at several places across the continent strengthen, however, the possibility that at least some species that are now extinct survived somewhat later than the Mungo evidence suggests, so the problem demands further clarification.

The Mungo burial was a cremation. Its date must have been around 25,000 BP, which makes it possibly the earliest known example of cremation in the world. The ritual involved smashing the charred bones and interring them in a circular, shallow grave—the Tasmanians practised similar methods of disposal, as is testified both by excavated data and by nineteenth century eyewitness accounts of cremation. Although it may seem rash to claim a behavioural continuity spanning 25,000 years, this possibility does merit consideration. It is relevant that Tasmanian stone assemblages, whose makers were isolated by the rising sea level some 12,000 years ago, belong to the same "Australian core tool and scraper tradition" as defined by the Mungo archaeologists (*World Archaeology*, 2, 52; 1970). This tradition is represented at all Australian Pleistocene sites so far investigated, and implies a technological and geographic continuum which may turn out to be more apparent than real once detailed regional ecological studies are available in the Mungo style.

All artefacts found eroding from the Mungo stratigraphic unit are encrusted with carbonate, as are several ochre pellets collected on the surface at the burial site and therefore presumed to be of that age. Human agency must explain their transport and some artistic function is clearly implied; this suggestive clue may be supplemented by the occurrence of quantities of ochre at Kenniff Cave, Queensland, soon after 19,000 BP. There is more substantial evidence at Koonalda Cave, South Australia, where some abraded grooves and finger markings on the wall are older than 20,000 years. Is Palaeolithic art really a European monopoly?

Innovations at Mungo extended beyond middens, mortuary rites and aesthetics. Rocks are a rare commodity

on these plains, and at site 3, "several lumps of baked clayey sand" served as substitute cooking stones about 30,000 years ago—the earliest pottery perhaps? From this same drainage system there are modern ethnographic parallels for baked clay used in this fashion. Another unconventional artefact, following the usual Neolithic interpretations, is Allen's discovery that the grindstone was utilized here, possibly 15,000 years ago. Pushing non-evidence somewhat, the inferred case for the world's earliest watercraft strengthens. If people settled at site 2 at about 32,000 BP, their ancestors must, earlier still, have possessed watercraft capable of crossing the tens of miles of sea separating greater Asia from greater Australia. Indeed *Homo sapiens sapiens* just possibly voyaged to Australia before he reached the New World or even Europe.

One of the most challenging discoveries is that the Mungo female is fully modern and Bowler, Thorne and Polach conclude their communication by emphasizing their chronological control of the cremated bones. Consequently, the date of the ancestral Aboriginal landfall on the Australian coast could parallel the age claimed for the Niah skull (40,000 years) and make this a conservative estimate for the date at which *Homo sapiens sapiens* appeared in south-east Asia.

The question of the status of the early Aboriginal population has been rendered more complex by another of Thorne's investigations. He recently announced (*Nature*, 238, 316; 1972) the discovery of an extensive burial ground associated with a lunette at Kow Swamp, more than 200 miles from Mungo across the riverine plains. The intriguing point is that the Kow Swamp population (one of the largest samples of fossil man known) exhibits traits which are "archaic"; its age is about 10,000 years. Analysis of cranial morphology suggests to Thorne that features of *Homo erectus* survived, yet this group is some 15,000 years more recent than the modern cranial form at Mungo and no significant topographic or environmental barriers separate these populations.

Australian scientists in these and other collaborative projects feel a sense of excitement when they consider the potential of the unstudied material. Their urge to correct Eurocentric texts in several disciplines may evoke echoes of Texas, with the

"oldest this" and the "most important that", but the nub of the matter is that these discoveries are being made, and they are being made by young research workers.—D. J. M.

BIOLOGICAL CHEMISTRY

Bilayers in Blood Serum

from a Correspondent

THE phospholipid bilayer, now confirmed as the basic molecular arrangement in membranes, may also be the structural basis of the low density lipoproteins in human blood serum according to Mateu *et al.* (*J. Mol. Biol.*, 70, 105; 1972).

It is frequently thought that X-ray diffraction can only be of value in molecular biology if the molecules under study can be crystallized, but this is not the whole truth. High quality crystals are required for studies of the atomic arrangement within molecules but interest is turning also to the arrangement on a molecular level in native biological systems. Because these structures are on a larger scale than atomic structures, they are frequently detected by electron microscopy, but often they do not survive the rigours of specimen preparation required for this technique and even the survivors have a debatable relationship with the *in vivo* structure. X-ray diffraction has been successfully applied in studies of membrane structure, even in the absence of perfect crystals, because the molecular arrangement in the membrane itself possesses elements of crystallinity. It has also proved possible to stack membranes side by side to form regular arrays which can give sharp diffraction patterns. In principle, however, if any system such as a membrane contains a general structural feature in which electron densities occur in constant relation to each other, the X-ray diffraction method can provide useful information.

Membranes from many sources have now been shown to contain a phospholipid bilayer, in which the lipid molecules pack in parallel register with each other; this generates a layer with all the phosphate groups on one side and the apolar rods on the other. Two such layers then pack with their apolar sides in contact to form a bilayer, and protein molecules are attached to this bilayer, albeit in a manner which is not yet fully understood.

Human blood serum contains many soluble lipoproteins, chief among which are the so-called low density lipoproteins (LDLs) of density 1.019 to 1.063 g cm⁻³. The probable implication of the LDLs in arteriosclerosis emphasizes their biological importance. LDL occurs in the form of spherical particles of average diameter 220 Å, and electron microscopy has already revealed that

twenty globular subunits, arranged in a dodecahedral pattern with icosahedral symmetry, occur on the spherical surface.

Mateu *et al.* have used small angle X-ray diffraction to study solutions of LDL particles, and as the individual LDL particles are not regularly arranged in the dilute solutions used, the diffraction patterns obtained yielded information about the electron density within a spherically averaged single particle. They carried out experiments on LDL in different concentrations of sodium bromide so that, by varying the electron density of the medium, certain structural features could be revealed and the phase problem resolved.

The diffraction patterns showed a series of intensity maxima with no zeroes of intensity between them. The result of applying plausible corrections was, however, a series of maxima separated by zero intensities; the bands were allocated alternate signs for the phases of their scattering amplitudes. These signs and amplitudes were then used to construct an electron density contour along a line corresponding to a radius through the spherically averaged LDL particle. This curve contained a striking and surprising feature—a trough of low electron density at a radius of 65 Å flanked by two high density peaks of about equal height. This, the authors suggest, indicates that the particles contain a phospholipid bilayer centred on a radius of 65 Å with the phospholipids distributed equally on both sides of the bilayer on the average.

Finally Mateu *et al.* propose a model in which the LDL particle consists of a protein core, a phospholipid bilayer and a surface network of proteins. Predictions made by the model agree well with the X-ray results, and although these results cannot discriminate clearly between models, the evidence in favour of the bilayer arrangements is interesting. It reveals the bilayer as a standard arrangement even for lipoproteins in particles which apparently are chiefly convenient forms of transport, and prompts the question whether this structure in LDL has any further significance.

PROTEINS

Sorting Out Symmetries

from our Molecular Biology Correspondent

A SIMPLE method, with as yet unrealized potential for the study of the relationship between subunits in proteins, is to introduce covalent cross-links with a suitable reagent, and examine the number and distribution of oligomeric products by detergent-acrylamide gel electrophoresis. The possibilities in this approach, as regards determination of the number of sub-

units per molecule, were first perceived and demonstrated by Davies and Stark, who devised a peerless reagent, or class of reagents, for the purpose. These are the dicarboxylic acid imido-esters, which are highly reactive towards primary amino groups, work in aqueous solution under mild conditions and contain a flexible paraffin backbone, which allows the maximum efficiency of cross-linking. Most work to date has been done with the suberic acid derivative (eight carbons), dimethyl suberimide. There are now signs that protein chemists are taking these reagents to their bosoms, for the realization has dawned that a detailed examination of the distribution of the different oligomers in the reaction product may be capable of revealing more about the structure than just the number of subunits (though even that is nothing to be scoffed at).

An adumbration of the kind of information that one might hope would emerge from carefully designed experiments is to be found in a paper by Carpenter and Harrington (*J. Biol. Chem.*, **247**, 5580; 1972). They have examined on detergent-acrylamide gels the products of cross-linking with dimethyl suberimide of bovine lens leucine aminopeptidase. There has been some disagreement about the number of subunits in this protein, which has a molecular weight of 320,000. Exposure to the cross-linking reagent leads to the appearance of six bands (including the monomer) in the electrophoresis, which supports the bulk of the earlier evidence, in favour of six identical subunits. They do not appear in anything like the same concentrations, however: dimers and tetramers showed strongly, whereas the trimer, and especially the pentamer, components were very faint. This already permits some inferences about the arrangement of the subunits within the hexamer. With the assumption of symmetry—that is to say structural equivalence of identical subunits—one can envisage four schemes, one of which can be excluded on the basis of the results. This is the planar heterologous hexagonal arrangement, with six-fold symmetry, in which all subunit interfaces are equivalent.

In such a case, although the relative weight of the different oligomers will depend on the extent of cross-linking, there is nothing to militate against trimers and pentamers. In the isologous planar hexamer, on the other hand, where alternate subunits are reversed, so that each makes a different kind of contact with either of its neighbours and the rotational symmetry is three-fold, the preferential formation of dimers, by way of one preferred type of interface, and then of multiples of dimers, can readily be visualized.

Other possibilities are the two forms of a dimer of trimers. The trimer will take the form of an equilateral triangle, and two such arrangements may associate in the eclipsed or in the rotationally staggered form, leading to a trigonal prism and an octahedral geometry respectively. The former would have three, and the latter four, distinct types of inter-subunit contacts. The authors have not attempted to take the analysis further by examining the predictions from these models for possible relative concentrations of oligomers.

Aspartate transcarbamylase is now an old chestnut, but two new papers lead to a more firmly based model for the relationship between the six catalytic and six regulatory subunits. Davies and Stark did in fact show, by the use of dimethyl suberimide, that the former were trimers and the latter dimers. Now Cohlberg *et al.* (*Biochemistry*, **11**, 3396; 1972) have excluded any possibility that the formation of dimers by the regulatory subunit is adventitious, by making cross-linked dimers, using dimethyl pimelimide, purifying them, and showing that a hydrodynamically normal enzyme results when these are mixed with the catalytic component. They find, moreover, that the regulatory subunits containing zinc are stable dimers in solution, whereas in the absence of zinc, monomers are in evidence. Taken together with the results of some superior electron microscopy by Richards and Williams (*ibid.*, 3393), a fairly explicit geometry for the whole protein has been deduced.

The electron micrograph of the enzyme dried in thin stain layers reveals three globules, presumably catalytic subunits, in the form of an

equilateral triangle. Outside this is another triangle rotationally displaced by 60° from the first, the apices of which are evidently pairs of regulatory subunits. In thicker stain the molecules appear to lie on their sides, and there is a clear gap between two layers, each presumed to contain three catalytic subunits, in the form of eclipsed triangles. Cohlberg *et al.* note that the two catalytic trimers seem not to be in contact, and in the absence of regulatory dimers have no tendency to associate in solution. Moreover, as the regulatory subunits do not associate beyond the dimer, there should be no important contacts between dimers. The model, which is based on these considerations, and conforms with the crystallographic requirement for both three- and two-fold symmetry, consists of V-shaped arms of regulatory dimers, each linking two catalytic subunits in the upper and lower triangle, which are related by a 120° rotation.

A striking case of functional control by subunit interaction is described by Segal and Stadtman (*Arch. Biochem.*, **152**, 356; 1972), working with the twelve-subunit hexagonal enzyme, glutamine synthetase. The activity is regulated by adenylation of subunits, which apparently occurs in a random manner, and the enzyme is stimulated by divalent metals. The effect of cobalt is of particular interest. It promotes the activity of the unadenylated enzyme, but it turns out that the resulting level of activity is not linearly related to the degree of adenylation (which it is in mixtures of a slightly and an extensively adenylylated preparation). Instead it correlates with the number of unsubstituted chains adjacent to other unsubstituted chains, calculated on the

RNA Virus Genomes lack Poly(U) Tracts

THE widespread belief that the tracts of adenylic acid residues to be found at the 3' terminal ends of some messenger RNA molecules of eukaryotic cells and their viruses are added after the RNA has been synthesized by RNA polymerase and are not, therefore, specified by complementary poly(dT) or poly(U) tracts in DNA or RNA genomes rests on circumstantial evidence, as Marshall and Gillespie stress in next week's issue of *Nature New Biology* (November 8). They also point out that, at least in mammalian cells, there are quite long stretches of A-T base pairs in the nuclear DNA, and the possibility that the poly(A) tails of cell messengers are genetically coded cannot be summarily dismissed.

Because of their size and complexity the genomes of animal cells do not readily lend themselves to detailed analysis, but the genomes of various

animal RNA viruses are sufficiently small for an experimenter to be able to detect and locate tracts of poly(U), which, if they exist, might code for the poly(A) tails of the messenger RNAs of these viruses. Marshall and Gillespie have, therefore, used labelled poly(A) as a probe in hybridization experiments for any poly(U) tracts in the genomic RNAs of some eleven oncogenic and non-oncogenic RNA viruses which replicate in mammalian cells of various species. Apparently none of these RNA virus genomes hybridize significantly with poly(A) in conditions optimal for specific poly(A)/poly(U) hybridization. Of the viruses Marshall and Gillespie have tested, three—Sendai virus, Newcastle disease virus and vesicular stomatitis virus—produce in infected cells messengers with poly(A) tails; these tracts must be added to messengers after transcription.

assumption of random distribution of adenylyl groups between the subunits of the dodecamer. The same law applies to activation dependent on alanine at low substrate levels. The catalytic behaviour is therefore evidently controlled in an unusual manner by heterologous interaction between subunits.

NUCLEOLUS

Gene Expression

from our Cell Biology Correspondent

DURING the past several years Henry Harris and his colleagues at Oxford have consistently championed the idea that the nucleolus, far from being simply an assembly site for ribosomal subunits, plays a crucial part in the expression of probably all structural genes in eukaryotic cells. This idea stems, of course, from the series of experiments, done by Harris and his associates, which have probed the reactivation of chicken erythrocyte nuclei after they are introduced, by cell fusion mediated by inactivated Sendai virus, into the cytoplasm of actively metabolizing cells of other species, notably cultivated mouse fibroblasts. The results of these various experiments showed that the transfer of detectable amounts of labelled RNA from erythrocyte nuclei to the cytoplasm of the heterokaryons, the appearance in that cytoplasm of chick proteins and the appearance in the reactivated erythrocyte nuclei of nucleoli are more or less coincident events. Not until erythrocyte nucleoli have appeared can newly made chick RNA and protein be detected in the cytoplasm. Harris and his colleagues have argued that this correlation is neither fortuitous nor the consequence of a species-specific restriction of translation of chick RNAs, but rather that a functional nucleolus is essential for the transfer of messenger RNAs from nucleus to cytoplasm. The group's latest experiments reported by Deák, Sidebottom and Harris (*J. Cell Sci.*, **11**, 379; 1972) certainly seem to confirm this interpretation of their accumulated data.

Deák *et al.* prepared heterokaryons by fusing chick erythrocytes with mouse A9 cells, which lack inosinic acid pyrophosphorylase (IPP) activity. They then inactivated all or some of the nucleoli in individual heterokaryons by microbeam ultraviolet irradiation and as controls left some heterokaryons unirradiated or irradiated at some other site in the erythrocyte nucleus. They then compared the appearance of chick IPP activity in these variously treated heterokaryons. To cut a long story short they find that in heterokaryons, all the erythrocyte nucleoli of which have been inactivated, IPP activity decays after nucleolar irradiation, whereas if

one or more erythrocyte nucleoli are left intact IPP activity appears and is maintained. Clearly these data indicate first that IPP is continually being turned over and that continued synthesis of the enzyme depends on a functional nucleolus in the reactivated chicken erythrocyte nucleus.

The appearance and maintenance of chick specific surface antigens and chick cell receptors for diphtheria toxin at the surface of heterokaryons also apparently depend on the integrity of the erythrocyte nucleoli. It is highly improbable that the structural genes for all these markers of chick gene expression are clustered around the nucleolus and are, therefore, inactivated directly by the irradiation procedure; by far the simplest interpretation of these results is that messenger RNA precursors, no matter where they are synthesized in the nucleus, must pass through the nucleolar region of the nucleus where perhaps they are processed and packaged before moving to the cytoplasm.

The experiments of Deák *et al.* depend, of course, on the technique of cell fusion mediated by Sendai virus, and the same is true of the experiments reported by Darzynkiewicz and Chelmiczka-Szorc (*Exp. Cell Res.*, **74**, 131; 1972) who have analysed DNA repair synthesis in the nuclei of ultraviolet irradiated chicken erythrocytes fused with HeLa cells, rat fibroblasts and fibroblasts from patients with xeroderma pigmentosum. They find that, within 16 h of fusion with HeLa cells and rat fibroblasts, repair DNA synthesis can be detected in the chick erythrocyte nuclei but not, of course, in the dormant nuclei of unfused erythrocytes. Furthermore, this repair synthesis, the rate of which increases as the chick erythrocyte nuclei are progressively reactivated, does not apparently depend on the transcription and translation of erythrocyte DNA, and it does not occur after the erythrocytes are fused with xeroderma pigmentosum fibroblasts, which are genetically incapable of DNA repair. These experiments prove, of course, that DNA repair is not a highly species-specific process; human and rat repair enzymes can apparently diffuse into chick cell nuclei and repair chick DNA.

ANTARCTIC

Effects on Man

from a Correspondent

THE first symposium on human biology and medicine in the Antarctic was held at the Scott Polar Research Institute, Cambridge, from September 19 to 21. The programme included sessions on physiological and psychological aspects, microbiology and clinical studies. The opening papers by Sir Vivian Fuchs,

Director of the British Antarctic Survey, and A. Stephenson, a veteran of polar travel, dealt with polar exploration yesterday and today; their contributions were followed by one from Professor A. Asahina (Japan) who described the little known Japanese Antarctic Expedition of 1911–12.

Work carried out at different national bases was reviewed by G. Budd (Australia), J. Rivolier (France), I. Tikhomirov (USSR), H. Yoshimura (Japan) and J. Shurley (USA). Acclimatization to cold occurred in members of an Australian base, according to Budd who described changes in the response of body temperature to a standard cold exposure test at Melbourne before departure, at intervals in Antarctica and on return to Mawson. His findings have been confirmed in more recent observations. A. Rogers (USA) could not, however, find any indication of acclimatization to cold in members of the Trans-Antarctic Expedition, whose clothing records he had analysed.

Several speakers emphasized the effects of heavy muscular work in the cold—sweating and heat discomfort—and D. Wilkins (Britain) described experiments at Halley Bay which showed that men develop acclimatization to heat during and following sledging journeys. The high level of energy expenditure in the Antarctic, according to J. Brotherhood (Britain), was due not only to the arduous work of man-hauling but also to the cost in terms of energy of essential tasks such as digging snow for water or to gain access to stores. Although it turns out that there is wide variation between individuals, men living at Halley Bay expended 3,000 to 3,500 kcalorie a day. R. Shephard (Canada) estimated, in a brief account of a comprehensive study of an Eskimo community, that Eskimo hunters expend energy at a similar rate. This implies a high level of food intake, with a large proportion provided by fat, and has prompted studies of blood lipid levels. G. Budd (Australia) and D. L. Easty (Britain) reported that they had found little change throughout the year in levels of serum cholesterol.

Professor Asahina contrasted the traditional dietary pattern with that at Soyara base in the Antarctic. In Japan, 15 per cent of the energy expended is derived from fat (compared with approximately 40 per cent in Britain), but in the Antarctic this increases to 27 per cent. Blood cholesterol levels of members of the Japanese base, although initially significantly lower than in either the Australian or British expedition members, rose throughout the Antarctic year to similar or even higher levels.

A very marked fall in the level of ascorbic acid in blood was observed by the Japanese; I. Tikhomirov (USSR) also emphasized the need for a greatly

increased intake of ascorbic acid during the polar winter. (It may be recalled that the death of Captain Scott and his companions has recently been ascribed once more to scurvy.)

Medically, the Antarctic seems to provide an environment that is dangerous because of extreme cold, winter darkness and isolation, but safe from the point of view of microorganisms which would seem to be almost absent from this sterile continent. D. J. Lugg (Australia), P. Doury and S. Pattin (France) and R. M. Lloyd (Britain) described methods of medical selection, the causes of illness, and so on. Accidents are, in all cases, the most important category, both in number and severity. In spite of the great changes in the technology of Antarctic life and travel, it is far from being a safe place, and the mortality rate in a young and highly selected group is substantial.

The sterility of Antarctica presents the microbiologists both with opportunities and challenges. When a ship leaves a group of men at an Antarctic base they are, in most cases, marooned for nearly a year. For one or two weeks they will have coughs and colds, then they are usually quite free of infection until a year or so later when they are relieved; most of them then develop severe colds. Does the antibody level decline during the period of isolation? T. R. Allen and M. J. Holmes (Britain) have shown that this does not occur, and the severity and frequency are presumably due to exposure to one of the very large number of viruses responsible, to which the individuals concerned have not become immune.

Low environmental temperature is the most obvious characteristic of the Antarctic environment, but there is also the long polar night and the long polar day, and the isolation of small groups at the various stations maintained by as many as twelve nations. The effects of these factors on human behaviour were described in a part of the symposium organized by E. K. E. Gunderson (USA), who outlined the selection techniques he and his colleagues have developed. The chief factors concerned are emotional stability, task compatibility and social compatibility. At first, selection tests correlated poorly with performance in the field, but effective selection tests have gradually been evolved and are now proving to be useful. L. Crocq (France) considers there had been an increase in psychological problems at French bases as they had become more comfortable, but I. Tikhomirov (USSR) thinks that both medical and psychological difficulties diminished at the Russian stations with successive physical improvements. J. Shurley (USA) emphasized the value of polar stations for behavioural studies, as observations

in a confined situation over a period of a year could and did yield a mass of information that is difficult to obtain in any other way. He also described the results of studies on sleep at the south polar station.

Sleep disturbance is frequently reported by United States personnel, and is described as "big-eye". It has been found that the extent of stage 4 sleep, the "deepest" level, gradually diminished and, after approximately six months at the south pole, was almost absent. Even more remarkably, on return to the United States stage 4 sleep remained at a very low level for periods up to a year. At present, it is not clear whether this changed pattern is due to a combination of the effects of the polar environment and the effects of the high altitude of the south pole. Some of the physiological changes observed both at the south polar station and at Vostock, the USSR station on the plateau, are clearly due to altitude, but more work is evidently needed to identify the combined effects of altitude, extreme cold, isolation and the changing pattern of light and darkness.

There were a number of papers dealing with studies in Arctic regions, specifically Alaska, Canada and Norway, and, at an informal discussion, ways in which Arctic-Antarctic collaboration could be developed were debated.

MOLECULAR BIOLOGY

How DNA is Replicated

from our Molecular Genetics Correspondent
LAST week, I discussed progress in showing that episome replication in *Escherichia coli* is under the same sort

of control as that of the bacterial chromosome. Several other articles in the September issue of the *Proceedings of the National Academy of Sciences* also illustrate the concern of molecular biologists to solve the central problem of how DNA is replicated. On page 2570, Olsen, Staudenbauer and Hofschneider show that *dnaB* mutants of *E. coli* cannot replicate the double stranded form of phage M13 DNA, although they can convert the infective single strands to replicative double strands. *DnaB* mutants appear to be defective in some cellular property concerned with the cell membrane, which lends further support to the idea that replication of M13 DNA involves membrane bound intermediates.

Also concerned with the *dnaB* mutants, Schekman *et al.* (*ibid.*, 2691) present the latest of their series of articles on the role of RNA in initiating replication of DNA. Their previous work has concentrated on phage M13, replication of which is inhibited by the addition of rifampicin, an inhibitor of RNA synthesis. They now turn their attention to ϕ X174 DNA, replication of which is not inhibited by rifampicin, *in vitro* or *in vivo*.

The single stranded form of the phage can be converted to double strands in a cell-free extract system, but extracts of the *dnaA* and *dnaB* mutants that are sensitive to temperature are inactive at high temperature. A combination of the extracts is active, which suggests that the *dnaA* and *dnaB* mutations affect different enzymes. This system is proving useful as a means to isolate the *dnaA* and *dnaB*, by purifying the extracts of one mutant strain which

ATP Hydrolysis and Restriction Endonuclease

IN *Nature New Biology* next week (November 8) Yuan, Heywood and Meselson report experiments which lead to the interesting speculation that the hydrolysis of ATP to ADP is required to maintain *Escherichia coli* K restriction endonuclease in a configuration which enables this enzyme to recognize its substrate, unmodified DNA. *E. coli* K restriction endonuclease cleaves DNA which has not been modified by replication in *E. coli* K cells. For example it cleaves unmodified lambda phage DNA into five roughly equally sized pieces and of course this enzyme provides *E. coli* K cells with a defence against foreign DNAs.

Yuan *et al.*, who found that the activity of this endonuclease depends amongst other things on a supply of ATP, noticed that as the endonuclease is purified an ATPase activity purifies with it. This ATPase has the same pH optimum as the endonuclease activity

and similar requirements, including the presence of unmodified DNA. In other words one molecule seems to have two enzymatic activities, an ATPase activity as well as an endonuclease activity. Moreover, they noticed that the hydrolysis of ATP continues long after nucleolytic attack of DNA has ceased, and about 10^5 ATP molecules are hydrolysed for every lambda DNA molecule that is cleaved.

Why does this endonuclease require to hydrolyse ATP if it is to cleave unmodified DNA, and why are so many ATP molecules hydrolysed? The energy released by the hydrolysis of so many ATP molecules is unlikely to be required for the nucleolytic reaction, not least because many other nucleases do not show this requirement. Yuan *et al.* suggest that the energy provided by the ATP may be required to maintain the endonuclease in an unstable configuration in which it can recognize its substrate.

confer activity upon the other. It will be particularly interesting to see how these proteins relate to the membrane changes in the mutant cells found some time ago by Siccaldi, Shapiro, Hirota and Jacob (*J. Mol. Biol.*, **56**, 475; 1971).

Although rifampicin fails to inhibit replication of ϕ X174, actinomycin D does so *in vitro*, as does deprivation of the four ribonucleoside triphosphates. RNA seems to be covalently linked to DNA in the product of replication. This supports the idea that RNA may be involved in the initiation of ϕ X174 replication, although previous attempts to implicate it have failed. This means that both M13 and ϕ X174 may use similar, although not identical, mechanisms. The insensitivity of the ϕ X174 process to rifampicin suggests that some enzyme other than the usual RNA polymerase may be implicated in providing RNA used for initiation, as indeed it may be involved in starting off the Okazaki fragments of bacterial DNA (see *Nature*, **239**, 7; 1972).

Turning to higher organisms, Stavrianopoulos, Karkas and Chargaff (*ibid.*, 2609) report further studies on the DNA polymerase which they have purified from chicken embryos. This is a small enzyme—the smallest DNA polymerase yet isolated—of only some 27,000 daltons. As this enzyme also requires the mediation of RNA as a primer for replication, it seems likely that RNA priming may be used by many, if not all, replicating systems to start off DNA synthesis.

(*Bull. Volc.*, **32**, 189; 1968) that the island represents a very early stage in the evolution of an oceanic island arc.

The simple picture of the Scotia Sea as a crustal remnant resisting the westward motion of South America and Antarctica is, however, inconsistent not only with the lack of seismicity along the northern and southern edges but also with a preliminary magnetic analysis by Barker (in *Antarctic Geology and Geophysics*, edited by R. J. Adie; 1971) which concluded that the Scotia Sea was formed almost entirely during the past 40 million years. Moreover, Barker's data complicated the picture even more by suggesting the presence of an active spreading centre, trending slightly west of north, to the west of (that is, behind) the arc-trench. Barker thus concluded that the region between the arc-trench and the newly postulated spreading axis forms a separate small plate (the Sandwich plate) growing and spreading eastwards at a rate of about 5.4 cm yr⁻¹ (the half spreading rate at the axis being 2.7 cm yr⁻¹).

Because the quality of the original data was poor, Barker has revisited the scene to acquire better results with which to examine the proposed spreading centre (*Earth Planet. Sci. Lett.*, **15**, 123; 1972). The new data, based on several east-west traverses across the north-south magnetic anomalies, confirm the presence of the postulated spreading centre. Moreover, a detailed analysis of the anomalies shows, first, a variable spreading rate with a minimum

around 2 million years ago, second, an overall acceleration of the spreading rate from 5 to 6 cm yr⁻¹ 4 million years ago to 7 to 9 cm yr⁻¹ today, and third, that during the past 4.5 million years at least, the spreading in the north has been significantly asymmetrical. It seems that during this period the spreading rate to the east of the axis has been greater than to the west. A similar asymmetry is also observed in the south out to 2.0 million years; but beyond 2.0 million years in the south and 4.5 million years in the north the data are not precise enough either to resolve any asymmetry or to exclude it.

As Barker points out, there is no reason to suppose that the motions over the rest of the Antarctica-South America boundary are anything but slow, nor any reason to suggest that relative motion is now occurring across the North Scotia Ridge. The conclusion must therefore be that the relative motions at the spreading axis and the trench are directly complementary, and thus that trench and axis form the leading and trailing edges, respectively, of a small separate lithospheric plate growing at its western edge and moving eastwards relative to South America at a rate of 7 to 9 cm yr⁻¹.

But the reason for this equality, which seems to be necessary in terms of the plate tectonic relationships in the area, is not immediately clear because the axis and trench are not part of the same spreading system in the sense that, say, the East Pacific Rise and the Aleutian Trench are. Barker's spreading axis lies

SEAFLOOR SPREADING

Scotia Axis Confirmed

from our Geomagnetism Correspondent

SMALL though it is, the Scotia Sea, which lies between South America and Antarctica, has been a happy hunting ground for geophysicists for several years. It is bounded on the east by the curved South Sandwich Island arc and trench, on the north by the North Scotia Ridge which reaches westward from the northern end of the arc-trench to the tip of South America, and on the south by the South Scotia Ridge which stretches westward from the southern tip of the arc-trench to the Antarctic Peninsula. It has usually been regarded as a remnant of the Pacific plate, even though the two components of the Scotia Ridge are only slightly active seismically and thus not particularly typical plate boundaries. The arc-trench system, on the other hand, is intensely active, the seismicity being consistent with a descending lithospheric slab dipping to the west. The older exposed basaltic volcanics on the South Sandwich Island have been dated in the range 0.7 to 4.0 million years, which ties in with Baker's view

X Linkage of Human Galactosidase

MEN who suffer from Fabry's disease are deficient in the enzyme galactosidase and their mothers either have a normal amount of this enzyme or are also deficient in it. These findings indicate that a deficiency of this enzyme is the result of a mutation linked to the X chromosome; they do not, however, prove that the structural gene for a galactosidase is X-linked and indeed in some mammals, horses and donkeys, the galactosidase gene is autosomal. To find out whether or not this is the situation in man Grzeschik and eight collaborators in the United States, Germany, Italy and Holland have used the by now familiar technique of inter-specific somatic cell hybridization. And as they report in next Wednesday's *Nature New Biology* (November 8) their experiments show that in all probability human galactosidase is X-linked.

Grzeschik *et al.* fused Chinese hamster cells deficient in thymidine kinase with human diploid fibroblasts lacking hypoxanthineguanine phosphoribosyl transferase and used HAT

medium to select hybrids. They then screened the hybrid cells for the presence of human galactosidase and three other human X-linked markers, and for three human autosomal markers during their cultivation in appropriate media. In summary they found that hybrid cells which retained human galactosidase also retained the three X-linked markers, and that loss of galactosidase correlated with loss of these three markers. By contrast segregation of galactosidase was independent of the segregation of the three autosomal markers. The simplest interpretation of these and other data is that the galactosidase structural gene(s) is X-linked in man.

Chasin, as he reports in next week's *Nature New Biology*, has also used the technique of somatic cell hybridization to investigate the linkage relationships of induced mutations of Chinese hamster cells, and he has reached the conclusion that at least three of the recessive mutations and their wild type alleles that he has studied are not in any way linked.

behind the arc-trench; and the descending lithosphere dips towards the axis. On the other hand, this geographical relationship encourages a comparison of the east Scotia Sea with the marginal basins of the western Pacific, which Karig (*J. Geophys. Res.*, **75**, 239; 1970) has suggested are extensional features. The similarities lie in position, size, topography, and depth; but there are also contrasts. According to Karig, extension is only associated with trench regions where earthquake foci extend to below 350 km, whereas beneath the east Scotia Sea trench only foci at depths less than 170 km have been recorded. Moreover, no symmetric or near symmetric magnetic anomaly patterns have yet been found in the Pacific marginal basins. These differences may or may not turn out to be important; but Barker clearly believes that analysis of the similarities between the two areas may lead to new insights in the future.

Taking the comparison a little further, it is possible to speculate even at this stage on the earlier history of the Scotia axis-trench system. For example, in spite of the present equality in the lithospheric production and consumption rates, have both axis and trench necessarily always been active simultaneously? It is very possible that the western Pacific trenches can exist quite independently of the volcanic activity behind them; and the evidence implies that this may have happened in the Scotia region too. The volcanic islands are young, their ages being consistent with their lying on a crust 5 to 7.5 million years old, and lie directly to the east of lithosphere 5 million years old. By contrast, the western side of the axis seems to have been spreading for at least 7.5 million years. This, and other evidence, suggests that the island arc and even the trench may well have existed before the present spreading episode began.

Finally, the speculation is not all one way. Barker suggests that in spite of Karig's explanation of the apparent lack of linear magnetic anomalies in the western Pacific basins in terms of diffuse intrusion over a wide area, such anomalies may yet be found. If they are, it will be interesting to see whether they share the asymmetry characteristic of the new Scotia axis.

CHEMISTRY

How to Educate

from a Correspondent

No cherished beliefs about practical work in chemistry were left unquestioned during the one day symposium on chemical education which was held as part of the Chemical Society's annual meeting in Nottingham between September 25 and 28. One county

council representative, playing Devil's advocate, suggested that abolition of individual practical work in schools would reduce the cost of each new comprehensive school by £30,000.

Professor A. K. Holliday (University of Liverpool) deals with the present state of practical chemistry in schools, the effects of the new curricula and the limited availability of time, equipment, and staff; he also questioned some of the presuppositions about practical work at this level. A similar exercise at the tertiary level was performed by Dr H. R. Tietze (University of Newcastle, Australia), who had interviewed a number of course designers and operators. It was felt that many students lacked motivation, yet many experiments seemed to consist basically of a sheaf of notes. Any possible complacency about a student-staff consensus on the objectives of practical work was demolished by Miss M. MacCallum (University of Glasgow), who had surveyed the first year practical chemistry courses at Glasgow as part of her honours degree. She found alarmingly little agreement between students and compilers of experiments about the objectives of each experiment. When students were told the objectives they tended to find the experiments more interesting and enjoyable, she said.

Dr C. J. Harding (Open University) remarked that his students came from

what was, academically speaking, a peculiar background — they probably had no previous experimental experience. The Open University had decided that experimental work was essential for a science course, and much ingenuity had gone into the design of home experiments; integration of theory and practical was easy, for each student was to have his own kit. Dr Derek Hoare (University of Dundee) described the validation of a scheme at the University of Monash in which 900 first year students, most of them not majoring in chemistry, undertook project work. A residential project week for sixth formers recently held at his school was enthusiastically reviewed by Mr M. Tomlinson (Ashby Boys' Grammar School). A wide range of pure, applied, and "social" projects was tackled, apparently with much success.

Dr. J. C. Mathews (University of Lancaster), concluding an authoritative survey of objectives and evaluation in school practical work, wisely observed that "systematic monitoring of teacher opinion may have more influence for change than any amount of teacher representation on committees". The consumer viewpoint, an assessment of the needs of the potential industrial chemist, was presented by Dr. A. C. Farthing (ICI Organics Division). Stressing the inculcation of a sense of

Closed Time and Black Body Radiation

CLOSED, oscillating universes have long been popular models, in spite of difficulties in relating them to the real universe. In next Monday's *Nature Physical Science* (November 6), Davies overcomes some of the inherent difficulties by producing a neat model in which the "3 K" background is explained as accumulated starlight from the cycle subsequent to the one in which we live. This curious state of affairs can arise, it seems, if the "arrow of time" is reversed in each cycle of the universe — that is, time flows backwards in the cycle which "follows" our own.

Many people have speculated on how the laws of physics might vary from one cycle to the next in a universe which expands from a very dense state, collapses, and repeats the cycle indefinitely. One stumbling block is that such models require a means of conserving entropy; Gold has proposed that entropy might be reversed in the collapsing and expanding stages of each cycle, but Davies's idea that entropy is reversed for each adjacent cycle is more attractive because the "time" at which reversals occur is better defined.

How does this idea account for the black body radiation? Radiation (starlight) which plunges into the hot, con-

tracting fireball between cycles will be scrambled, as will the matter, until all correlations and information are lost. When the radiation re-emerges, therefore, it will have the form of an isotropic background. The origin of this background will be in the cycle "after" our own, because of the reversed arrow of time in that cycle. Even better, because the starlight in that cycle must have much the same energy density as the starlight in our cycle, the long unexplained "coincidence" in the energy density of the black body background and the energy density of starlight is no longer a mystery.

"We have," says Davies, "a picture of two temporal regions with oppositely directed time sense, separated by a small region in which there is no direction of time." If this model had been put forward ten years ago, the discovery of the "3 K" radiation would have been taken as remarkable confirmation of its validity; even now, coming after the empirical observation of a cosmic background, the model has great aesthetic appeal (as do all steady state models) and has the merit, not shared by many cosmologies, of being tied directly to a measurable physical property of the universe.

hazard, he caused some uncomfortable shuffling by asking how many of the participants in the symposium already have a death certificate signed by poor laboratory techniques. Dr D. A. Mathewes (Western Carolina University) gave a delightfully stimulating account of his classes in what can only be called remedial chemistry; Britain's use of 'Alka-Seltzer' has obviously been too unimaginative.

The most thought-provoking paper came from Dr Richard Whitfield (University of Cambridge). Since 1966 the International Association for the Evaluation of Educational Achievement has been studying science achievement among pupils and students in three age ranges (10+, 14+ and 17+) in twenty different countries. Detailed results will be published later this year (by Almqvist and Wiksell/John Wiley) and they are certain to cause controversy, for they have direct social and political implications. In all countries, variables connected with the cultural environment of the student determine his or her achievement in science to a far greater extent than variables connected with teaching.

MOLECULES

Microwave Spectroscopy

from a Correspondent

THE continuing need for regular meetings on microwave spectroscopy was the motivation for the Second European Microwave Spectroscopy Conference, held at the University College of North Wales, Bangor, on September 18 to 22. This meeting was supported by the Royal Society, through its European Science Exchange programme, and about 140 scientists from fourteen countries, almost equally divided in their formal allegiance between physics and chemistry, gathered to discuss minute details of molecular anatomy and energetics, which, at this degree of magnification, can expose the lameness of generalizations which chemists are inclined to take for granted.

The measurement of radio spectra of gases at wavelengths between about 10^{-1} m and 10^{-3} m has been one of the principal sources of detailed knowledge of molecules for twenty-five years. The past decade has, however, seen a rapid expansion of such work in Europe at a time when molecular spectroscopy in general has become too diverse to serve, without subdivision, as a basis for useful meetings. The first conference on a European scale devoted entirely to microwave spectroscopy was duly held, also at Bangor, in 1970.

The interaction of molecular rotation with internal molecular motions of large amplitude is now a dominant theme in about half the current work. Professor

E. Hirota (Kyushu University, Japan) described outstanding contributions to the analysis of spectra, complicated by such interactions, in terms of unusual force-field information. It is perhaps not widely known that there are variations of orders of magnitude in the energies required to rotate or invert groups within molecules, and to bring about other conformational changes, and that information on such details is elusive to the point of requiring prolonged investigation and computation. The rate of acquisition of such information is now increasing rapidly. In other invited talks, Dr J. K. Tyler (University of Glasgow) discussed inversions of the NH_2 group and their dependence on chemical structure, while Professor I. M. Mills (University of Reading) dealt with anharmonicity effects in force fields with special reference to microwave studies. The closely related contributions of rotational spectroscopy to precise knowledge of molecular geometry were illustrated in an invited lecture by Dr L. Nygaard (University of Copenhagen) who reviewed the distinguished work of the Copenhagen group on ring structures. Among recent advances in the elucidation of molecular electron distributions, none has been more outstanding than those made through the study of the microwave Zeeman effect, and Dr W. H. Flygare (University of Illinois) reviewed how these methods have sharply cast new light on familiar themes. The parts of molecules in which the positive and negative ends of their electric dipoles lie can now be found directly from experi-

ment, while such terms as aromaticity and antiaromaticity can be quantified in terms of measured parameters in the electron distribution.

There was considerable interest in the latest experimental advances. These included not only commercial instrumentation and analytical microwave spectroscopy, but also several sophisticated developments, notably that of a computer controlled spectrometer described in an invited talk by Professor W. Zeil (University of Ulm).

In a programme of sixty-seven contributed papers, emphasis followed the general areas covered by the invited talks, but other aspects such as the spectroscopy of molecules in outer space, time-dependent effects in which processes of energy transfer are observed, and the shapes and intensities of spectral lines, were also represented. Microwave spectroscopists, perhaps through a past sense of isolation, form a very "clubbable" group of people who enjoy their conferences more than most.

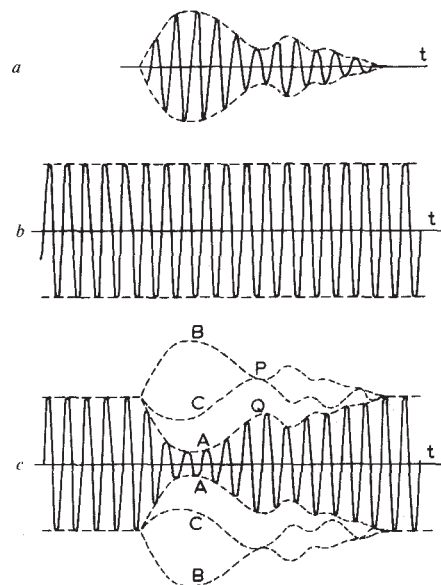
Europe has become one of the chief areas of activity in this field, competing effectively with the United States. To use terms familiar to all who study rotation spectra, this would have displaced the centre of gravity of such work to somewhere in the middle of the Atlantic, were it not for the simultaneous rapid developments on the other side of the world in Asia and Australia. While it is clear that conferences on a world scale are a regular requirement, it is important that, within the continent of Europe, a firm decision has been made to hold regular specialist meetings.

Probing the Antarctic Ice Sheet by Radio

IN next week's *Nature Physical Science* (November 6), Nye, Berry and Walford describe how the technique of radio echo sounding may be adapted so that changes in the thickness of the Antarctic ice sheet can be measured to an accuracy of about 5 cm. What they have done is to reflect a pulse of radio waves (~ 35 MHz) off the bedrock beneath the ice and then mix the returned pulse with a continuous wave from the oscillator. The result is a modulation of the continuous wave that is sensitive to the vertical position of the transmitter and receiver (and therefore to the thickness of the ice). The diagram shows the effect of various relative phases.

It is already well known that the position of a transmitter-receiver system can be located in a horizontal plane relative to the bedrock by noting the exact shape of the returned pulse. This changes markedly over horizontal distances of 5 m or so—the wavelength of the radio waves in ice—and the position can again be assessed to about 5 cm.

Nye and his colleagues point out that an accuracy of 3 parts in 10^9 would be



required in measurements of g —which essentially compare distances to the centre of the Earth—to obtain the same sensitivity.

Climate and the Galapagos Islands

PAUL A. COLINVAUX

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Data from the El Junco lake suggest that the climate of the eastern Pacific Ocean in glacial and postglacial times correlated with climatic events in the northern hemisphere.

THE Galapagos Islands lie at the edge of the Central Pacific dry zone¹ (Fig. 1), being essentially without rain from May to December². The drought is a result of reduced circulation under a stable inversion maintained by cool ocean water, but is broken in the early months of each year when the inter-tropical convergence retreats briefly to a position south of the geographic equator. Warm water and atmospheric mixing then bring rain to the Galapagos and the South American coastal desert, a phenomenon known as El Niño. Animals and plants of low lying parts of the Galapagos must be adapted to living for much of the year with no more water than can be obtained from thin fog (the *garua*), but the higher parts of larger islands penetrate the inversion and are capped by stratus clouds, providing a wet fog-drip environment in which cloud forests and even peat bogs form. If the global climate pattern was different, as it might have been in an ice age, the effects on the Galapagos and their biota should have been pronounced, and a record of the climate of the Galapagos of the past would be of great interest. Accordingly, I have searched the archipelago for lakes and bogs, coring the deposits I found^{3,4}. I have been able to obtain a history from times too old to be dated by the radiocarbon method to the present day.

On the summit of San Cristobal (Chatham), at an altitude of about 650 m by our pocket altimeter, the hill known as El Junco is capped by an explosion crater holding a lake. A panoramic photograph of the lake has already been published³, and a colour plate of the lake is included in a recent book⁵

A circular body of water, about 270 m across and 6 m deep, laps against the rim of the crater, which is rounded, deeply weathered, and nowhere much higher than 20 m above lake level. An overflow ditch 3 m deep and 2 m wide has been cut through the lowest part of the rim, but no water flowed through it during my visit (July 1966). Apart from this overflow, and possible seepage through the rim, the lake basin is closed. The only catchment area is the inside of the crater rim itself, suggesting that the lake level, or even the very existence of the lake, should be sensitive to changes in the precipitation-evaporation ratio. I have no measurements of the water budget of El Junco, but it seems likely that much of the water collects during the annual rainy season and that the water is then hindered from evaporating during the rest of the year by the blanket of stratus clouds.

Three cores through sediment under the lake end against a stratum sufficiently hard to deform steel cutting bits on my Livingstone coring device, suggesting that the rock floor of the crater was reached. The cores suggest that the sediment body is roughly cone shaped, with the greatest thickness being 15.35 m (Fig. 2). There are three chief stratigraphic units. The bottom of the basin is filled with a red clay-rich mineral deposit, which does not look like lake mud. This is interrupted in one of the cores by an interval of gyttja, 0.5 m thick and beautifully laminated with black and brown bands, apparently the deposit of an ancient pond. The pond or lake was evidently smaller than modern El Junco because the deposits were only penetrated by one of the cores. Radiocarbon determinations from the top and bottom of this ancient gyttja give ages of >34,300 and >48,000 yr BP (I-6043; Y-2555). The third stratigraphic member is a layer of banded gyttja more than 3 m thick which everywhere overlies the red clay. The oldest radiocarbon determination obtained at the transition between the red clay (which does not contain carbon for dating) and the upper body of gyttja is 10,170 ± 140 yr BP (I-4173). Twenty-four more radiocarbon dates in the gyttja

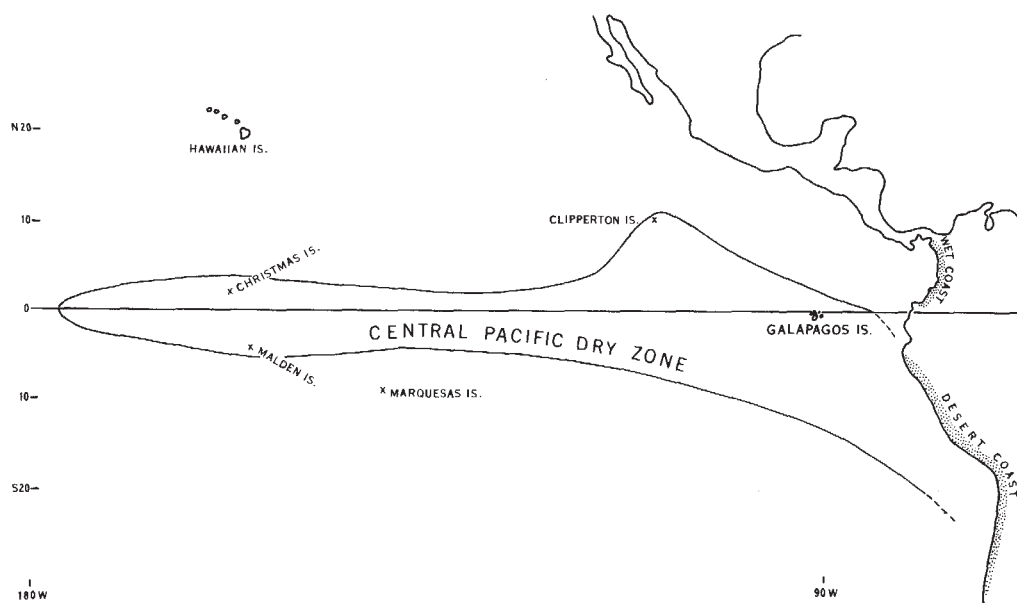


Fig. 1 Sketch map of the eastern Pacific Ocean, showing the approximate boundaries of the Central Pacific Dry Zone during the months of the boreal summer. The Intertropical Convergence lies to the north of this zone. Zone boundaries after Palmer and Pyle¹. Boundaries of coastal desert after Trewartha².

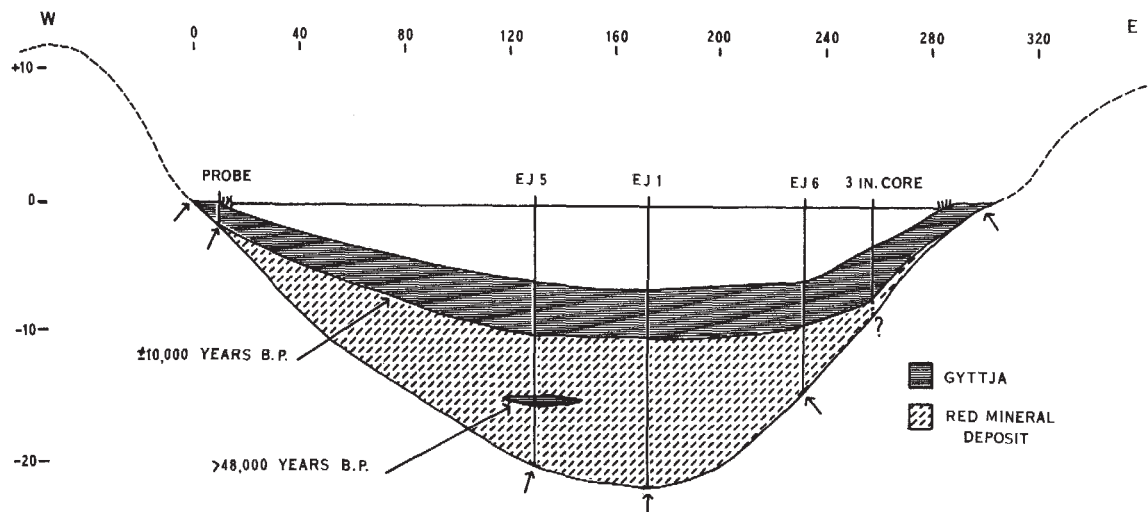


Fig. 2 Diagrammatic cross section of the crater of El Junco on a line roughly running west-east. The overflow outlet is near the right of this diagram, being a 3 m deep trench through a low point of the crater rim. Soundings were made with rods from a rubber boat. Horizontal measurements were made by stretching a line across the crater and measuring along it in arm lengths. Short arrows mark the points at which the rock floor of the crater was identified by drilling or at the water's edge. Vertical exaggeration is 5 : 1.

body reveal no anomalies, suggesting undisturbed and continuous deposition to the present day.

The stratigraphy of the El Junco deposits suggests four stages in the history of the basin (Fig. 2)—an early episode when non-lacustrine red clay deposits collected in the basin, an interval of ponding at a time too ancient to be dated by the radiocarbon method, another long interval without standing water in the basin when red clay continued to collect, and the establishment of the modern lake 10,000 yr ago. It is of great interest to ask if the two episodes of ponding with the deposition of gyttja were responses to climatic change, because if so there is a suggestion here of the rhythm of glacial events in the north. More than 34,000 yr ago, a time which could very well be that of the last non-glacial episode, El Junco held a small lake. Then, throughout the time of Classical Wisconsin and later Würm glaciations, there was no lake. Finally, a lake formed in early postglacial time and has persisted since.

A basin may fail to hold a lake because breaks in its structure allow water to drain away, or because water evaporates faster than it is precipitated. In El Junco these alternatives are complicated by the possibilities of volcanism either through ash deposits or through heating. The rupture and drain hypothesis is the more cumbersome because it requires mechanisms both to close vents at the onsets of ponding and to open them again when lakes drain. For an essentially closed basin such as this, an hypothesis of evaporation is simpler to sustain on the principle of parsimony, but the various possibilities can be tested by mineralogical examination of the red clay deposit.

X-ray diffraction of samples of the red mud⁴ suggests a mixture of amorphous clays with scattered concretions of gibbsite and haematite, and reveal no traces of minerals such as montmorillonite, illite, or goethite which might have formed under water. X-ray diffraction thus suggests that the clays are the products of weathering in an oxidizing environment, and that the red colour is caused by simple amorphous hydrates of iron and aluminium. This general conclusion is consistent with the results of an informative examination by thin section of a series of samples of the red deposits by W. L. Kubiena (private communication). Kubiena reported that his thin sections revealed "a very dense clayey, originally yellow-coloured sediment stained by peptized amorphous iron hydroxide". Further, the clays were the products of weathering of basaltic rocks or tephra because magnetic grains had been well preserved in the fabric. This is a satisfactory conclusion because rocks exposed on the rim of El Junco are basalt and the Galapagos volcanics are known to be basaltic. Flow lines

revealed in the thin sections suggest that movement down to the crater floor was at least partly by water.

It seems likely that most of the red mineral deposit can be accounted for in terms of weathering of the walls of the crater itself or accretions of tephra which once blanketed the crater. Assuming that the red mass is cone shaped, with a basal diameter of 190 m and an apex of 11 m, the volume of the red mud turns out to be about 104,000 m³. If the inside of the crater rim above the top of the red deposit is thought of as an annulus 50 m wide, it would only have to lose 2 m of its surface to account for this volume. Falls of tephra over the entire area of the crater need be less than 1 m thick to account for it. I tentatively conclude, therefore, that the red mud was produced by accretion of tephra, and by weathering of the rim of the crater, in times when there was no standing water in the basin but when occasional showers served to wash the deposit down the slopes and promote the weathering of clays.

There was no lake in El Junco when the red mud collected, but was this because the climate was arid or because regular rain washed through the deposit and drained away through some fissure that opened when the ancient pond became extinct? There was an interval of more than 24,000 yr between the end of the ancient period of ponding and the onset of the modern lake 10,000 yr ago. If there had been much flow of water through the deposit for any significant portion of this interval, a soil should have formed. I have not been able to find traces of soil profiles in the three complete sections of the red deposit which my cores provide. Furthermore, Kubiena found that the fine particles were opaque, but if they had resulted from soil forming processes they should have been highly translucent as are the fine particles of all red soils. There is thus good reason to believe not only that there was no lake but also that there was too little water percolating through the basin for soils to form.

It is possible to conclude that the red deposit is the product of weathering of tephra and rocks of the rim of El Junco, in air, under an arid climate. Very rare falls of rain would be sufficient to wash loose material onto the crater floor. Perhaps the moistness of enveloping stratus clouds would be sufficient to promote the formation of the amorphous clays. There was too little precipitation for the soils to form, and no ponding in the crater for this long period because the climate was too arid.

I suggest that soon after the crater of El Junco formed a moist climate like that of the present allowed a pond to form on the basin floor. This lasted for many years but eventually a drier climate caused the water to dry up. This dry climate persisted for more than 24,000 yr, being replaced by comparatively

moist climate of the present some 10,000 yr ago when the modern lake formed. Evidence from microfossils contained in the two bodies of gyttja supports this interpretation. In the ancient gyttja are many pollen grains of the water plant *Myriophyllum*, a plant not known from the Galapagos. Pollen of *Myriophyllum* is not present in the upper body of gyttja from El Junco nor from any of the other polliniferous Galapagos deposits of the last few thousand years which I have examined. There is a suggestion here that, when the ancient El Junco pond dried up, *Myriophyllum* was eliminated not only from that pond but also from any others in the archipelago to which birds might be expected to have carried it. But more striking still is the evidence for the history of species of the water fern *Azolla*. *A. microphylla* now lives in ponds all over the archipelago, including El Junco, and its distinctive spore massulae are present throughout the upper gyttja body. But in the ancient gyttja are massulae of a different species, *A. filiculoides*, not now known from the archipelago. There is a strong suggestion here that something eliminated *A. filiculoides* from the entire archipelago when drying of the old El Junco pond destroyed the local population, just as the ancient population of *Myriophyllum* had been destroyed. When wetter times at last returned 10,000 yr ago chance dispersal from South America brought a different species of *Azolla* to pre-empt the niches afforded by Galapagos ponds⁶.

The combined evidence of gross stratigraphy and fossil

water plants suggests that the past 10,000 yr have been a comparatively wet episode in the Pleistocene history of the Galapagos, that this episode was preceded by a long drought embracing all the time of the last glacial advance, and that earlier there was another comparatively wet period. What climatic changes might have caused that prolonged drought?

It is tempting to look for an answer in the system which maintains the cloud cover on El Junco and other highlands. The wet dripping fog which these stratus clouds provide must certainly do much to prevent evaporation from El Junco and other ponds. In the absence of cloud cover these shallow bodies of water should quickly dry up. But the stratus clouds are a consequence of the very inversion which denies the Galapagos rain for most of the year. Any change which removed this inversion and its associated stratus clouds would bring convection circulation, cumulus clouds, and rain to the Galapagos. It must be concluded that the inversion was also present in the remote past and that the higher islands retained their caps of fog in which forest plants and animals could live. This suggests that during the ancient drought the annual rains of the El Niño periods must have failed. If the rains of December to May were then much rarer El Junco and ponds everywhere would indeed have dried up. The rains come when the intertropical convergence makes its annual retreat to the geographic equator. The record from El Junco suggests, therefore, that between more than 34,000 yr ago and 10,000 yr

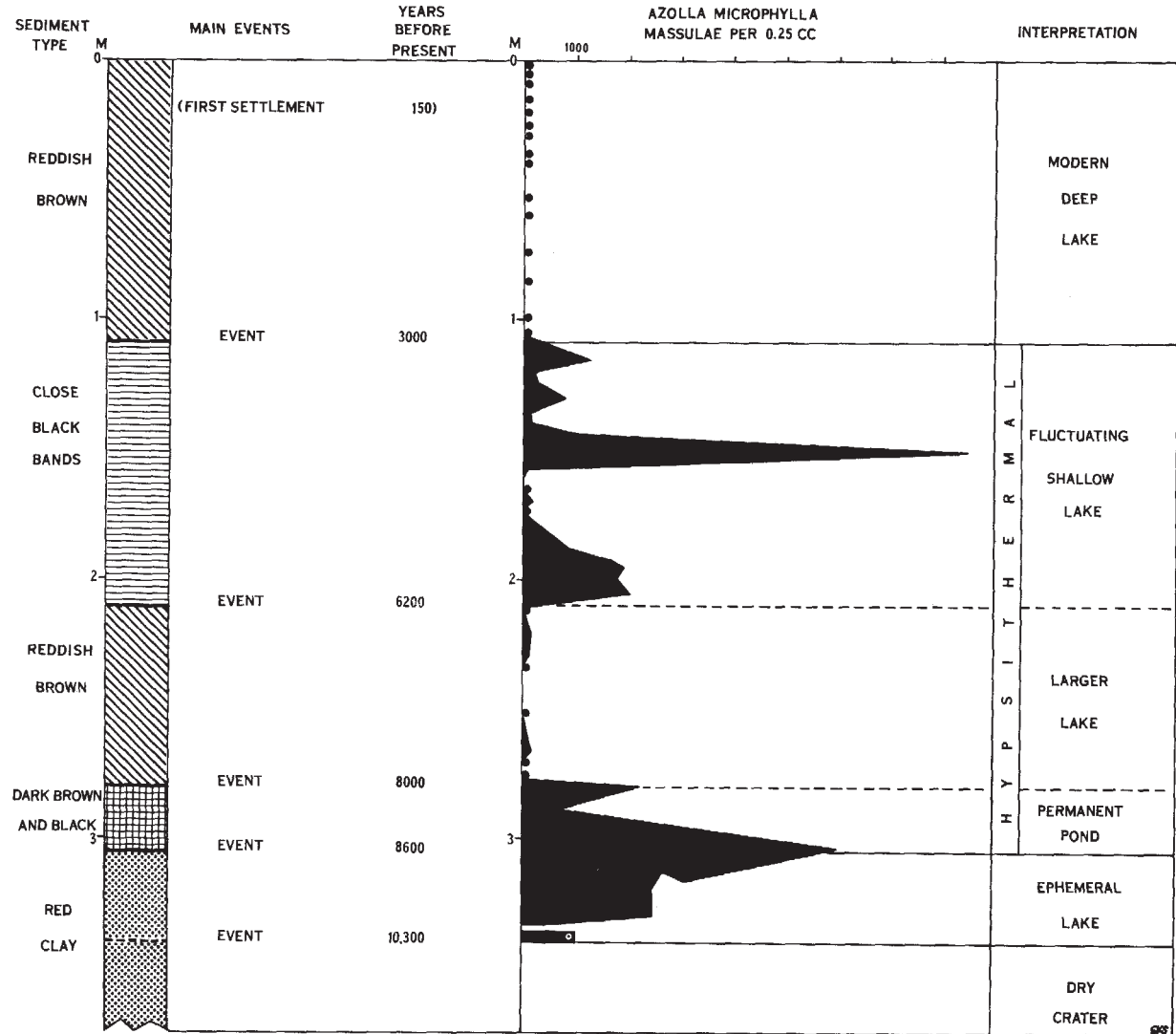


Fig. 3 Gross stratigraphy and content of *Azolla microphylla* massulae in the top 3.5 m of El Junco lake sediment. The stratigraphy is mirrored in two cores taken some 20 m apart near the middle of the lake. Dating of events is by radiocarbon determinations made separately on two cores and rounded off. A dot represents less than 150 massulae; each division represents 1,000. The interpreted history of the lake at the right of the diagram is derived only from gross stratigraphy and the implications of the *Azolla* counts.

ago the intertropical convergence remained north of the geographic equator almost permanently.

This climatic model is consistent with conclusions recently reached by Quinn⁷, who argues that exposing large areas of continental shelf between the Malay Peninsula and Australia by the eustatic lowering of sea level so affected the Southern Oscillation that the Central Pacific dry zone was extended in glacial times.

Unfortunately it is not possible to be certain about the dates of all the events recorded in the El Junco cores. All that can safely be said is that the early period of ponding predated the last advance of continental glaciers in the north, that there was no water in El Junco during the whole period of the advance and retreat of these continental glaciers, and that El Junco has held a lake for the past 10,000 yr. Yet, in spite of the absence of many positive dates, the suggestion of synchrony of Galapagos drought with glacial events does seem strong. It allows the tentative conclusion that the El Junco sediments record the effects of climatic changes in the equatorial Pacific Ocean associated with the advance and retreat of continental glaciers in the northern hemisphere. In glacial times the Galapagos were essentially without rain throughout the year, but there was an inversion with associated stratus clouds in the region, as at present. In interglacial and postglacial times the intertropical convergence came south to the geographic equator every year between December and May, bringing rain.

Both bodies of gyttja preserve a rich assortment of microfossils such as pollen, and both are banded in ways which suggest that they record histories of fluctuating lake levels. The well dated sequence of bands in the upper body allows a reconstruction of the history of the lake over the last 10,000 yr, giving evidence of the effects of a postglacial thermal maximum, or hypsithermal⁸, on the Galapagos.

The bands appear as blackish layers on a matrix of red-brown (Munsell 10YR 3/2). The surface mud of the modern lake, lying under 6 m of water, is of the same red-brown colour, as is all the top 1 m of the deposit. Black mud similar to that in the bands is found only in the shallow water under the emergent sedges at the edge of the lake; this suggests that the blacker mud was deposited when the lake was much shallower.

Support for this conclusion comes from the fact that black bands are rich in fossil massulae of the water fern *Azolla*, containing more than ten times as many of them as the red-brown mud. Water ferns, like duckweed, form dense growths on shallow waters, but survive only round the edges of larger deeper lakes. In modern El Junco, *Azolla* is only to be found inshore among emergent vegetation, but in the small ponds of the Santa Cruz (Indefatigable) tortoise reserve, *Azolla* may completely cover the water surface. This provides a strong inference that the blacker, *Azolla*-rich mud represents times of low lake level and that the reddish-brown mud represents deeper water like that of the present day.

The chief colour intervals in the mud of the past 10,000 yr, together with counts of the included *Azolla* massulae, are shown in Fig. 3. On the right is an interpretation of the size of the lake in each episode. The chronology rests on a cross correlation of the banding sequence in the two longest cores from the middle of the lake with radiocarbon dates. The closeness of the cross correlation is generally good, but it varies with different intervals. The distinctive dark brown and black interval close above the red clay has been independently dated in all three cores at $8,230 \pm 140$ (I-2868), $8,450 \pm 160$ (Y-2554), and $8,480 \pm 140$ (Y-2559) yr BP. The upper stratigraphic boundaries do not correlate as well, probably because the lake floor was uneven and allowed deep water to collect successively at the different sites. Nevertheless the events can clearly be recognized in the two longer cores, and the radiocarbon ages of them are comparable. What looks like the most dramatic later change in the lake's fortunes, the onset of the deep modern lake responsible for the top 1 m of sediment,

is bounded by radiocarbon ages of $3,920 \pm 140$ (Y-2552) and $3,030 \pm 100$ (Y-2544) yr BP.

The lake was probably permanent but shallow at 8,600 yr BP. There followed a period of fluctuating level, but the lake was generally shallower than now until 3,000 yr ago, when it became deeper; it has remained deep ever since. The dates of 8,600 and 3,000 yr BP are just those generally considered to bound the postglacial thermal maximum or hypsithermal interval⁸. Increased temperatures over a lake in a closed basin, which receives significant rain in only one season of the year, might well cause the lake to be shallow and fluctuating. Alternatively a thinning, or raising, of the stratus clouds which now shelter the summit of El Junco should produce the same effect, and such thinning of the clouds might well be a consequence of changing temperature. The record of banding in the El Junco cores thus suggests rather strongly that the warming of the hypsithermal interval was experienced in the Galapagos, their remote, oceanic, and equatorial site notwithstanding. The early part of the hypsithermal is, however, thought to have been the warmest part, but there was a period between 8,000 and 6,200 yr BP when the El Junco lake may have been nearly as deep as the lake of modern times. Perhaps this will reveal something about the way in which hypsithermal events influenced the atmospheric circulation over the Pacific.

The history of the El Junco lake suggests that the climate of the Galapagos and the eastern Pacific Ocean has fluctuated broadly in synchrony with glacial and postglacial climatic events in the northern hemisphere. Drought on the Galapagos during a time of glacial advance suggests that the intertropical convergence was then north of the geographic equator at all seasons of the year. That the climate of the Galapagos has never been wetter than now strongly suggests that the stable inversion which is a feature of the climate of the region has been present at least as commonly as at present for more than 48,000 yr. Increasing warmth during the postglacial hypsithermal interval seems to have affected the Galapagos even though the general pattern of atmospheric circulation must have been similar to the present one. These conclusions provide data useful for constructing tentative models of atmospheric circulation over the Pacific Ocean in the past.

The evidence that the Galapagos Islands were drier than now in ice-age times is important to an understanding of the evolution of the unique Galapagos plants and animals. There have always been cloudy places in the highlands where life of the wetter Galapagos elevations could maintain itself, but the absence of spring rains, like the absence of standing fresh water, must have been profoundly important in the lives of some species. Not only were the droughts of the more arid parts of the archipelago even more severe in ice-age times, but the areal expanse of the deserts was much increased by the eustatic lowering of sea level. If, as I suspect, the species diversity of the wet uplands in the Galapagos turns out to be less than the species diversity of the desert lowlands, this history of larger deserts in the past will be seen to be one of the contributory causes.

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Aspirin and Indomethacin Prolong Parturition in Rats: Evidence that Prostaglandins Contribute to Expulsion of Foetus

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Increase of stillbirths and adverse maternal effects in rats after administration of aspirin and indomethacin in the final days of pregnancy warns against their use in the late stages of human pregnancy.

A FUNCTIONAL role for prostaglandins in parturition is suggested by the increase of prostaglandin concentrations in human blood¹ and amniotic fluid² during labour and by the observation that exogenously administered prostaglandins can induce labour^{3,4} or abortion^{5,6}. This is not definite proof that prostaglandins are necessary for parturition or that they are the natural uterotonic substances mediating expulsion of the foetus. Mechanical stimuli⁷ such as uterine distension⁸ can promote prostaglandin production so that the increase in prostaglandin release during labour could be a consequence and not the cause of increased mechanical activity of the uterus. If endogenously formed prostaglandins play an essential role in parturition, one would anticipate that inhibitors of prostaglandin synthesis might adversely affect parturition when administered to pregnant animals. This hypothesis was tested by treating pregnant rats during the last few days of gestation with indomethacin or aspirin, both of which inhibit prostaglandin synthesis or release in several experimental preparations⁹⁻¹². The results indicate that aspirin and indomethacin inhibit prostaglandin formation in the uterus, reduce uterine motility, and prolong parturition, resulting in high foetal mortality.

Sixty Harlan-Wistar rats were obtained in the 18th to 21st day of gestation (gestation is about 22 days). The rats were

housed individually with bedding of light-coloured wood shaving. The sixty rats were divided into six groups of ten animals and drug treatment was started immediately. Two groups of ten were given indomethacin, 0.1 mg kg⁻¹ or 1.0 mg kg⁻¹ orally twice a day. Three groups of ten were given aspirin, 10, 30 or 100 mg kg⁻¹ p.o. twice a day. Aspirin or indomethacin was suspended in 1% methylcellulose such that each rat received 1 ml. kg⁻¹ of body weight by gavage at 7.30 a.m. and 3.30 p.m. Ten control animals received 1 ml. of 1% methylcellulose per kg of body weight twice a day.

The rats were under close observation during the daytime and the time when parturition started was noted. This was judged by birth of the first pup or by the beginning of excessive bleeding from the vaginal opening. Four to twenty hours after the beginning of parturition, the dams were sacrificed and the uterus and gastro-intestinal tract examined. Animals that gave birth at night were observed for 4 h the following day before they were sacrificed so that all dams were allowed at least 4 h from the beginning of parturition to give birth to their litter.

Of the ten animals in the control group (Table 1), six gave birth to their litter during the daytime. All six of these animals produced their litter in 3 h or less. Very little blood loss occurred during parturition. Mortality among offspring of the control dams was very low (Table 1), only 1 dead pup out of 138 born. On examination, two placental scars were unaccounted for but the contents of the gastro-intestinal tracts showed no ingested foetuses. Foetal mortality was therefore at most 3 out of 140.

Extended Parturition after Indomethacin and Aspirin

Two groups of ten animals were treated with indomethacin, 0.1 mg kg⁻¹ or 1.0 mg kg⁻¹, p.o. twice a day (Table 2).

Table 1 Controls 1% Methylcellulose Orally Twice a Day (1 ml. kg⁻¹)

Rat	Cumulative doses	Excessive bleeding	Duration of parturition in hours (N = born at night)	Alive	Born Dead	Number of offspring		Total	Ulcers
						In utero	when sacrificed		
						Alive	Dead		
C-1	3	—	1.5	15	0	0	0	15	—
C-2	6	—	N	17	0	0	0	17	—
C-3	5	—	3	8	1	0	0	9	—
C-4	3	—	1.5	13	0	0	0	13	—
C-5	2	—	N	15	0	0	0	15	—
C-6	4	—	N	15	0	0	0	15	—
C-7	3	—	<3	13	0	0	0	13	—
C-8	4	—	N	16	0	0	0	16	—
C-9	5	—	<2	11	0	0	0	11	—
C-10	3	—	3	14	0	0	0	14	—

Prior to the onset of parturition all twenty animals appeared healthy and normal. Three of the ten animals receiving the low dose of indomethacin and eight of ten animals receiving the high dose showed adverse signs during parturition, including excessive bleeding from the vaginal opening, prolongation of parturition to more than 4 h and a high incidence of foetal mortality (Table 2). Once it was clear that the duration of parturition was extended beyond the normal duration, the dams were sacrificed. Two rats receiving the low dose of indomethacin and seven receiving the high dose still had foetuses *in utero* (Table 2). Usually a large amount of blood was inside the uterus and the placentas of unborn dead foetuses were detached from the uterine wall whereas placentas of unborn live foetuses were attached. The cervix was dilated, even in animals 1-11 and 1-14 (Table 2), which had not given birth to a single pup even after more than 5 h of haemorrhaging.

Animals I-1, I-7 and I-9 (Table 2) showed characteristic vaginal bleeding, increased duration of parturition, and a high number of pups born dead. The remaining animals receiving the low dose of indomethacin were indistinguishable from controls. Amongst the pregnant rats receiving the high dose of indomethacin (Table 2), eight had an increased duration of parturition, of which six had excessive blood loss showing that bleeding did not always accompany extended parturition and foetal deaths (Table 2, I-18 and I-20). Conversely, one animal (I-15) that gave birth to all her pups alive in less than 2 h did have blood loss greater than that seen in controls.

If some foetuses had died before parturition started, the fact that the foetuses were immobile could have contributed to the prolonged parturition, since movement of the foetus probably aids expulsion. However, results from another group of pregnant rats treated with indomethacin suggested that the

Table 2 Indomethacin Orally Twice a Day in 1% Methylcellulose (1 ml. kg⁻¹)

Rat	Cumulative doses	Excessive bleeding	Duration of parturition in hours (N = born at night)	Alive	Born Dead	Number of offspring In utero when sacrificed		Total	Ulcers
						Alive	Dead		
Indomethacin 0.1 mg/kg									
I-1	8	Yes	> 6	0	5	0	8	13	Yes
I-2	5	—	1	13	0	0	0	13	—
I-3	3	—	N	14	0	0	0	14	—
I-4	3	—	2	13	0	0	0	13	—
I-5	4	—	2	10	0	0	0	10	—
I-6	5	—	3	14	1	0	0	15	—
I-7	5	Yes	> 4	3	5	1	3	12	—
I-8	4	—	N	13	0	0	0	13	—
I-9	3	Yes	> 6	3	8	0	0	11	—
I-10	3	—	N	8	0	0	0	8	—
Indomethacin 1.0 mg/kg									
I-11	3	Yes	> 5	0	0	7	8	15	Yes
I-12	3	Yes	> 7	6	5	0	2	13	—
I-13	3	—	N	8	1	0	0	9	—
I-14	4	Yes	> 5	0	0	6	8	14	—
I-15	6	Yes	< 2	6	0	0	0	6	—
I-16	2	Yes	> 7	5	4	0	1	10	—
I-17	2	Yes	> 5	1	1	3	8	13	Yes
I-18	4	—	> 4	7	3	2	2	14	Yes
I-19	2	Yes	> 5	9	4	0	0	13	Yes
I-20	5	—	> 5	13	1	0	2	16	—

Table 3 Aspirin Orally Twice a Day in 1% Methylcellulose (1 ml. kg⁻¹)

Rat	Cumulative doses	Excessive bleeding	Duration of parturition in hours (N = born at night)	Alive	Born Dead	Number of offspring In utero when sacrificed		Total	Ulcers
						Alive	Dead		
Aspirin 10 mg/kg									
A-1	5	Yes	> 4	16	0	0	0	16	—
A-2	2	—	N	12	2	0	0	14	—
A-3	2	—	N	11	0	0	0	11	—
A-4	3	Yes	5	14	1	0	1	16	Yes
A-5	3	—	N	8	5	0	0	13	—
A-6	8	—	N	14	3	0	0	17	—
A-7	7	—	3	11	0	0	0	11	—
A-8	4	—	N	6	0	0	0	6	—
A-9	3	—	3	8	3	0	0	11	—
A-10	1	—	> 3 < 4	9	3	0	0	12	—
Aspirin 30 mg/kg									
A-11	4	—	N	11	0	0	0	11	—
A-12	3	Yes	> 4	8	1	0	1	10	—
A-13	3	—	N	11	0	0	0	11	—
A-14	2	—	> 4	10	9	0	0	19	—
A-15	3	Yes	N	0	13	0	0	13	Yes
A-16	2	—	N	8	1	0	0	9	—
A-17	2	Died after two doses						14	—
A-18	4	Yes	N	10	2	0	0	12	Yes
A-19	6	Yes	3	8	5	0	0	13	—
A-20	8	Yes	> 4	0	14	0	1	15	—

foetuses died during, not prior to, parturition. Five dams (18–21 days pregnant) were given indomethacin (1.0 mg kg^{-1} orally, twice a day) for 2–3 days before parturition. They were sacrificed just before or immediately on observation of the first signs of parturition. In this group all 67 foetuses *in utero* were alive. This shows that the offspring died during parturition, possibly as a result of placental separation.

In animals receiving indomethacin the incidence of ulcers was relatively low and none had perforations of the gastrointestinal tract. Two dams receiving 0.1 mg kg^{-1} and four receiving 1.0 mg kg^{-1} had a few (2–6) scars approximately 1 mm in diameter on the gastric mucosa (Table 2).

In vitro studies^{9,12} indicate that aspirin is 50 to 1,000 times less potent than indomethacin as an inhibitor of prostaglandin synthesis. Therefore, a relatively high dose of aspirin was initially used in pregnant rats. However, eight out of ten dams receiving 100 mg kg^{-1} twice a day died after two doses of aspirin, before the onset of parturition. One out of ten died with 30 mg kg^{-1} twice a day. The cause of death was not apparent. None of the dead rats had perforations of the gastrointestinal tract. I do not wish to emphasize this datum here but it is noteworthy that deaths occurred in these pregnant rats with lower doses of aspirin than previously reported in non-pregnant rats^{13,14}.

One out of ten gravid rats (A–4) receiving aspirin at 10 mg kg^{-1} twice a day, and three out of ten (A–12, A–14, A–20) receiving 30 mg kg^{-1} twice a day showed adverse effects during parturition similar to those caused by indomethacin (Table 3). Others (A–1, A–15, A–18 and A–19) showed some, but not all, of the adverse signs. Several animals receiving the low dose of aspirin (A–2, A–5, A–6, A–9 and A–10) gave birth to some dead pups without excessive blood loss. Three of these five litters were born at night so it was not known whether parturition was prolonged. The other two litters were born within 3 h. Comparing the high number of stillborn foetuses to controls suggested that foetal death is the most sensitive measure of impaired parturition. Although there was no significant difference between the six groups of rats when the total number of offspring was compared, all five of the drug-treated groups had significantly fewer pups born alive ($P < 0.05$).

Dead pups found in cages after night-time birth could have died after parturition due to neglect; however, this seems unlikely since this was never observed with litters born during the daytime. Further experiments indicated that foetuses born dead to rats receiving the low dose of aspirin died during, not before, parturition. Five 18–20 day pregnant rats were treated with aspirin (10 mg kg^{-1} orally twice a day) for 2 or 3 days, and then sacrificed just before or at the first sign of parturition. None of the 63 foetuses *in utero* was dead. As with indomethacin, foetal deaths caused by aspirin probably occurred during, not before or after, parturition.

Prostaglandin Release from Uterus during Parturition

Vane and Williams¹⁵ demonstrated that indomethacin simultaneously inhibited prostaglandin release and spontaneous contractions of pregnant rat uteri *in vitro*. I designed experiments to show that aspirin, like indomethacin¹⁵, inhibited both contractions and prostaglandin release from pregnant rat uterus and that the oral doses of indomethacin that prolonged parturition were sufficient to decrease the ability of the uterus to produce and/or release prostaglandins.

Uteri taken from pregnant rats late in gestation (about 20 days) and placed in a tissue bath release prostaglandin-like material into the bath fluid¹⁵. The amount of PGE and PGF-like prostaglandins released into the bath fluid by uterine tissue taken from 18–19 and 20–21 day pregnant rats was compared with prostaglandin release from uterine tissue taken from rats during parturition.

Fig. 1 shows release from uterine tissue into the bath of PGE and PGF-like prostaglandins at three gestation times.

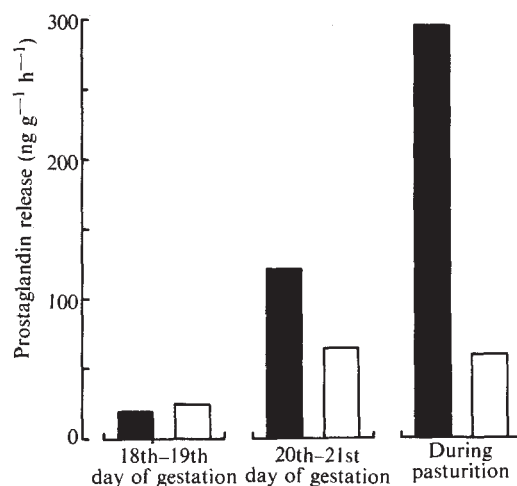


Fig. 1 Vertical columns show the rate of release of prostaglandin from isolated uterus taken from rats at three different times in the gestation period. The rate of release (in ng/g of tissue/h) was calculated from the amount of PGE-like and PGF-like material extracted from the bath fluid after a 30 min incubation period, separated by thin layer chromatography and bioassayed as either PGE₂ (□) or PGF_{2α} (■). Rats were sacrificed by a blow on the head and the uterine horns were opened longitudinally where the blood vessels enter. Three pieces of muscle (one from the ovarian end, one from the middle and one from the cervical end, each weighing approximately 1 g) were placed in three 10 ml. tissue baths containing Tyrode's solution gassed with 95% O₂, 5% CO₂. Contractions against a 3 g weight were detected by isotonic transducers and monitored on a rectilinear writing recorder. After a 30 or 60 min incubation in fresh Tyrode's solution, bath fluid from the three chambers was withdrawn, pooled and adjusted to pH 2 with 1 M HCl. The solution was extracted twice with 20 ml. of ethyl acetate and extracts pooled and extracted four times with 50 ml. of phosphate buffer, pH 8. The buffer extracts were pooled, adjusted to pH 2 with 5 M HCl, and extracted twice with 50 ml. chloroform. The chloroform was evaporated *in vacuo* to a volume of 5 to 10 ml. rinsed from the flask twice with 5 ml. of chloroform, and evaporated to dryness under nitrogen; the residue remaining after evaporation was dissolved in chloroform and separated by thin layer chromatography (TLC) using silica gel 0.25 mm thick and a solvent of chloroform (90%), glacial acetic acid (5%), and methanol (5%). All parts of the TLC plate were scraped, suspended in chloroform, eluted, and evaporated to dryness under nitrogen. The residue was dissolved in saline and the amount of prostaglandin-like activity was assayed simultaneously on the rat stomach²², rat colon²³, and chick rectum²⁴ superfused²⁵ with Krebs solution containing atropine ($0.1 \mu\text{g ml}^{-1}$), mepyramine ($0.1 \mu\text{g ml}^{-1}$), methysergide ($0.2 \mu\text{g ml}^{-1}$), propranolol ($3 \mu\text{g ml}^{-1}$) and phentolamine ($0.2 \mu\text{g ml}^{-1}$) in concentrations sufficient to block the effects of acetylcholine, histamine, serotonin and catecholamines, respectively. There was 60–65% recovery of authentic PGE₂ and PGF_{2α}. The biological activity from the TLC plate corresponding with an R_f for E prostaglandins was assayed to PGE₂ and the spot corresponding to F prostaglandins was assayed to PGF_{2α}. No attempt was made to separate PGE₁ from PGE₂ or PGF_{1α} from PGF_{2α}. There was 30–35% recovery of PGE₂ and PGF_{2α} through the extraction and TLC procedure.

Uterus taken from rats sacrificed during parturition produced about 20 times more PGE-like substance than uterus from 18 to 19 day pregnant animals. Release of PGE-like material remained relatively constant. Thus, there is a dramatic increase in production of a substance with physical, chromatographic and biological properties like prostaglandin F_{2α} but relatively little increase in PGE-like material at the time of parturition.

Orally administered indomethacin decreased the ability of uteri to produce prostaglandins. The uterus was removed from eight dams sacrificed during parturition. Four of these had been treated with indomethacin (1 mg kg^{-1}) twice a day and showed signs of extended parturition. The tissues were placed in Tyrode's solution. After 30 min, the solution bathing the tissues was withdrawn and the bath refilled and left for a second 30 min incubation period. A third collection of bath

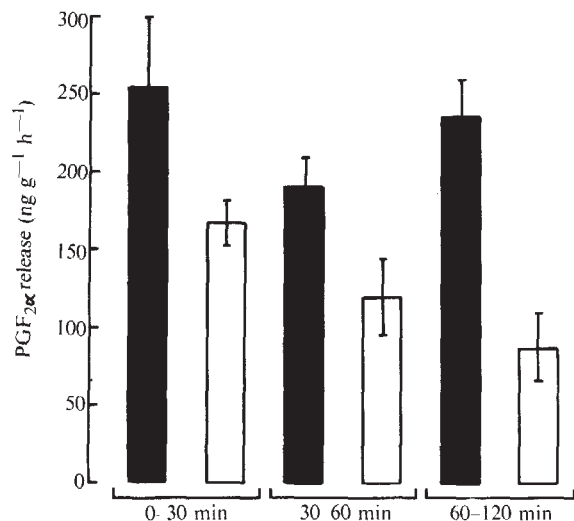


Fig. 2 Vertical columns show the rate of release of PGF-like material from uterus *in vitro* taken from rats during parturition. Acidic lipids were extracted from bath fluid after three incubation periods: 0-30 min after sacrificing the rat, 30-60 min and 60-120 min, and bioassayed as PGF_{2α}. Four rats were pretreated with indomethacin 1 mg kg⁻¹ orally twice a day for 2-3 days before the onset of parturition (□) and four rats were untreated (■). Vertical brackets show the standard error of the mean. There was significantly less PGF_{2α} released from uterus from indomethacin-treated rats than from controls at 30-60 min ($P < 0.05$) and at 60-120 min ($P < 0.01$) by Student's *t* test.

fluid was made for the incubation period between 60 and 120 min and extracted as in Fig. 1. As prostaglandin release from uterus during parturition was mostly PGF-like (Fig. 1), the prostaglandin-like activity in these samples was assayed on the isolated tissues directly after extraction without TLC chromatography, as PGF_{2α}. Fig. 2 shows release of PGF_{2α} into the bath for the three incubation periods. During the initial 30 min, the release of PGF_{2α} was high and was greater in the control animals than in the indomethacin-treated animals, but the difference was not statistically significant. However, during the 30-60 min collection period and in the 60-120 min collection period, the rate of prostaglandin release from uterus of indomethacin-treated rats declined substantially, and significantly, below that of the control animals ($P < 0.05$ in 30-60 min; $P < 0.01$ for 60-120 min). These results indicated that uterus from dams treated orally with doses of indomethacin sufficient to prolong parturition had a decreased ability to release prostaglandins when placed in a tissue bath.

All of the pieces of uterus taken from the control animals in Fig. 2 showed spontaneous contractions that began immediately after putting the tissues into the bath whereas 5 of the 12 tissues from indomethacin-treated rats had markedly less spontaneous activity showing that some regions of the uterus from indomethacin-treated rats had depressed muscle motility.

All of the animals of Fig. 2 showed a high rate of release of prostaglandin during the first 30 min, perhaps due to the trauma of killing the animal, removing the tissue and placing it in a new environment. However, uterus from control rats continued to release PGF_{2α} for 2 h. This probably represents release of newly formed prostaglandin whereas uterus from indomethacin-treated rats did not continue to release the large amount of PGF_{2α} evident in the first 30 min.

Prostaglandin release shown in Fig. 2 may have been abnormally enhanced by the mechanical trauma of removing the tissue from the animal, so I tested another simple method of estimating the ability of the uterus to produce prostaglandins in less severe conditions. When uterus from a pregnant rat is placed in a tissue bath and treated with adrenaline the tissue relaxes, but within 2 or 3 min the spontaneous activity returns¹⁶. Tothill, Rathbone, and Willman¹⁷ have shown that the recovery of spontaneous activity after adrenaline is due to

adrenaline-induced prostaglandin formation by the uterine tissue. Uteri from control and indomethacin-treated gravid rats were relaxed with adrenaline (Fig. 3). Within 3 min contractions of the uterus from the untreated animal (Fig. 3A) returned, but the uterus from the animal treated with indomethacin (Fig. 3B) remained relaxed for more than 30 min. Therefore, under conditions where adrenaline is known to induce prostaglandin production¹⁷ and cause a reversal of the inhibitory response to itself, pretreatment of the rat with indomethacin prevents this adrenaline reversal.

Aspirin inhibits Uterine Contractions

In vitro, when aspirin (100-300 μg ml⁻¹) was added to a tissue bath containing spontaneously contracting uterine smooth muscle from a 20-day pregnant rat, the contractions were diminished and prostaglandin release into the bath was reduced. These effects were similar to the effects of indomethacin on pregnant rat uterus described by Vane and Williams¹⁵. Their results with indomethacin were also confirmed in my study. Indomethacin (0.01-1 μg ml⁻¹) added to the tissue bath reduced or blocked spontaneous contractions of the uterus and, at the same time, reduced or abolished release of both PGE and PGF-like material. Papaverine (10 μg ml⁻¹) abolished contractions of the uterus *in vitro* but did not prevent prostaglandin release into the bath, indicating that blocking contractions *per se* do not prevent prostaglandin release.

I noted that to obtain maximum inhibition of uterine contractions *in vitro*, aspirin or indomethacin must be added to the tissue bath immediately after a wash. If the tissue was not washed just before adding drug, prostaglandin previously released into the bath remained in contact with the tissue in sufficiently high concentrations to support contractile activity. After blockade of contractions with aspirin or indomethacin (but not papaverine), addition of PGF_{2α} (5-10 ng ml⁻¹) or PGE₂ (5-10 ng ml⁻¹) to the bath restored spontaneous activity. As prostaglandin release can probably be equated with synthesis⁷, the results *in vitro* indicate that indomethacin and aspirin inhibit, simultaneously, prostaglandin production in the pregnant rat uterus and uterine contractile activity.

In vivo, the anti-inflammatory acids, aspirin and indomethacin, prolong parturition and at the same time uterine prostaglandin production and motility are decreased. Fenoprofen another anti-inflammatory agent of this type¹⁸, has been shown to inhibit prostaglandin synthesis in rat uterus *in vitro* and also prolong parturition *in vivo*, when given to rats in the final days of gestation (J. L. Emmerson and J. W. A., in preparation). The effects I describe may therefore be characteristic of all non-steroidal, anti-inflammatory acids.

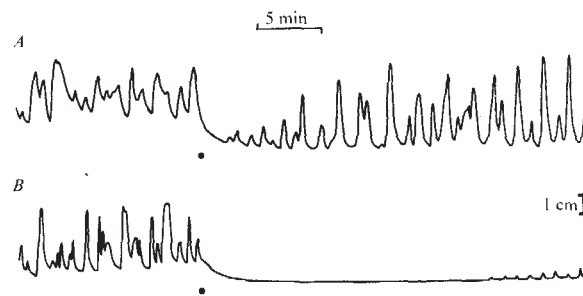


Fig. 3 Isotonic contractions of isolated uterus taken from two rats in the 21st to 22nd day of gestation. Uteri removed from an untreated 21 day gravid rat (A) and from a gravid rat treated with indomethacin (B) (1 mg kg⁻¹ orally one hour before sacrifice) were placed in tissue baths. The tissues were washed every half hour for two hours until both the control and the uterus from the indomethacin treated animal, which was initially relaxed, had similar spontaneous activity. At ●, both tissues were given a maximal inhibitory dose of adrenaline (0.1 μg ml⁻¹).

The reason for the high mortality in the offspring is unknown, but results indicate that deaths occurred during parturition. Excessive blood loss could have been one contributing factor to foetal deaths, especially if prostaglandins function as vasoconstrictors in the umbilical vessels, as proposed by Karim¹⁹. As excessive blood loss did not always accompany prolonged parturition and high foetal deaths, a more attractive explanation for foetal deaths is a reduced ability to expel the foetus, due to decreased uterine motility. My results therefore support the hypothesis that prostaglandins are required in parturition and suggest that F prostaglandins are essential for expulsion of the foetus.

Clinical Importance

How important are these effects of aspirin and indomethacin on parturition in rats considering what is known about prostaglandins and parturition in humans? First, the dramatic increase in PGF_{2α} in human amniotic fluid during labour² and the fact that prostaglandins can induce labour^{3,4} suggest that prostaglandins may be as important for parturition in women as they are in rats. Also, although it has not yet been demonstrated with uterus, aspirin or indomethacin both inhibit prostaglandin production in other human tissues^{10,20} at therapeutic dose levels. Therefore, the use of these anti-inflammatory substances late in pregnancy should be warned against, at least until further reports are available.

It has been suggested that an inhibitor of prostaglandin synthesis might be used to postpone premature labour²¹. It was not possible in the present study to determine whether the length of gestation in individual rats was increased, since the exact time of fertilization of each rat was not known (except for within 2 days). However, the mean cumulative doses given to each drug-treated group were not significantly different from the control group, suggesting that there was no delay in the onset of parturition. Therefore, nothing in the present data indicates that parturition was postponed, but rather only prolonged to a harmful degree. Thus, the present results suggest

that factors other than prostaglandin production may regulate the time of onset of parturition; however, once parturition has started, prostaglandins are required for expulsion of the foetus.

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The Macroscopic Level of Quantum Mechanics

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The problem of relating the quantum mechanical description of atomic processes to the behaviour of matter in bulk is resolved in a conceptually simple treatment.

Atomic theory raises the epistemological problem of harmonizing the detailed dynamical description of atomic systems given by quantum mechanics and the description of individual atomic processes and of the behaviour of matter in bulk at the level

of macroscopic observation. The logical side of this problem is completely elucidated by the recognition of relationships of complementarity between the two modes of description: on the one hand, there is the complementarity expressed by the indeterminacy relations, which governs the application of the macroscopic space-time localization and momentum-energy conservation to the individual atomic processes; on the other, there is the complementarity between the account of the behaviour of a large system of atomic constituents given by quantum mechanics (and electrodynamics) and the description of the same system as a material body in terms of the concepts of macroscopic mechanics, electromagnetism and thermodynamics.

The formal side of the problem, however, which consists in establishing the consistency of the rules connecting the formalism of quantum mechanics with the concepts used in the account of macroscopic observation, still leaves scope for a presentation more in accordance with the conceptual simplicity of the actual situation. A general treatment of the quantum theory of large atomic systems which satisfies this desideratum has been given in a recent article¹. The purpose of this note is to outline the method and the principal results.

The work pursued during the past decade by the Brussels group has clearly shown that the method best adapted to the investigation of large atomic systems is not the ergodic but the kinetic approach of statistical mechanics, applied to the limiting case of infinite systems (that is, systems of infinite degree of freedom, but such that the number of elements within a given phase extension has a finite limit). Because such systems have essentially a continuous energy spectrum, the vexed question of "coarse graining" can be ignored and the asymptotic limit of the density operator for times very large on the atomic scale, but finite, can be directly discussed. This discussion leads to the conclusion² that the time evolution of the system may be split rigorously into formally independent "subdynamics", characterized, in a manner presently to be explained, by certain projection operators depending on the correlations between the constitutive elements of the system. One of these subdynamics belonging to the projector $\tilde{\Pi}$ given by equation (7) below contains all the information about equilibrium properties and linear transport properties. We may therefore define the macroscopic level of description of quantum mechanics as the reduced description in terms of the variables of the $\tilde{\Pi}$ -subspace. That such a reduced description is at all possible results precisely from the fact that the $\tilde{\Pi}$ -subdynamics is expressed by an independent equation of evolution. The application of this analysis to the case of a measuring apparatus, initially triggered off by an interaction of atomic duration with an atomic object, shows in a surprisingly simple way that its evolution in $\tilde{\Pi}$ -space conforms to the "reduction" rule of quantum mechanics; this important conclusion follows directly from the mathematical structure of the $\tilde{\Pi}$ -subspace of the apparatus, which entails the elimination of the initial phase relations between the components of the density operator of the atomic object. Our paper contains a simple and general derivation of these remarkable results, which shows more clearly how these methods not only lead to a deeper understanding of the epistemological problems of atomic theory, but even to a significant extension of the scope of quantum mechanics.

In a superspace defined as the direct product of the Hilbert space and its dual, the density operator $\rho(t)$ appears as a supervector, varying in time according to a Liouville equation of the form

$$i\dot{\rho}(t) = L\rho(t)$$

The Liouville superoperator L may be expressed in terms of the Hamiltonian H of the system. For this purpose, we may use a convenient notation for the special class of "factorizable" superoperators $O \equiv M \times N$ depending on a pair of supervectors M, N according to the definition $O\rho = M\rho N$; we may then write $L = H \times 1 - 1 \times H$. Our aim being to find the long time effect of correlations, we must, to begin with, compare our system, defined by the Hamiltonian H , with a "model" system H_0 , from which the interaction energy V , responsible for the correlations, is removed, in such a way that $H = H_0 + V$. The eigenstates of H_0 form a complete orthogonal basis of representation in Hilbert space, from which we construct a similar basis in superspace: the latter may be divided into two classes of supervectors, those built up of pairs of identical (or physically equivalent) eigenstates, and those built up of pairs of different eigenstates; they belong, respectively, to two orthogonal subspaces of superspace, characterized by projection superoperators P_0, P_c . Then the projections $\rho_0 = P_0\rho$ and $\rho_c = P_c\rho$

of the density supervector correspond, respectively, to the average distribution densities and the correlation amplitudes. Putting $L_{00} = P_0LP_0$, $L_{0c} = P_0LP_c$ and so on, we obtain for ρ_0 and ρ_c the coupled Liouville equations

$$i\dot{\rho}_0 = L_{00}\rho_0 + L_{0c}\rho_c, \quad i\dot{\rho}_c = L_{c0}\rho_0 + L_{cc}\rho_c \quad (1)$$

The next step is to extract from these equations the asymptotic forms $\rho_0(t)$, $\rho_c(t)$ of ρ_0 and ρ_c for large positive values of the time variable: these are expected to express our possibilities of prediction of the future evolution of the system on the macroscopic time scale.

We must here restrict the generality of the Liouville superoperator in order to characterize the class of systems which we expect to exhibit the "normal" asymptotic behaviour, that is an approach to a state of equilibrium. To this end, we observe that the time evolution of the correlation density ρ_c is essentially governed by the superoperator $T_c = \exp(-iL_{cc}t)$, depending on the part of the Liouville superoperator which acts entirely in the correlation subspace. We assume accordingly that the asymptotic effect of this superoperator $T_c(t)$ upon any regular supervector A which is not an invariant is to reduce this supervector to zero: $\lim_{t \rightarrow \infty} T_c(t)A = 0$; we express by this assumption the fading of the system's "memory" of its correlations. This condition, which may also be expressed as an analyticity condition on the Laplace transform of $T_c(t)$, has first been verified in this form by a perturbation expansion, for infinite systems in whose description there enters a "small" physical parameter such as the coupling constant or the density³. More recently, it has been shown that for soluble models, such as the Friedrichs model, the analyticity assumption is satisfied rigorously (that is, independently of any perturbative approach) for a large class of interactions⁴. By means of this assumption, we readily derive from the second Liouville equation (1) the following relation between the asymptotic densities:

$$\tilde{\rho}_0(t) = \int_0^\infty d\tau e^{-iL_{cc}\tau} (-iL_{c0})\tilde{\rho}_0(t-\tau) \quad (2)$$

It has the form of an integral equation, showing how the asymptotic correlations build up by sequences of processes starting from the average situations through which the system passes in the course of time.

We now introduce an asymptotic time evolution operator by writing $\tilde{\rho}_0(t)$ in the form

$$\tilde{\rho}_0(t) = e^{-i\theta t} \tilde{\rho}_0(0) \quad (3)$$

The advantage of the representation (3) is to reduce the integral equation (2) to a simple linear relation between $\tilde{\rho}_0(t)$ and $\rho_c(t)$ taken at the same time:

$$\tilde{\rho}_c(t) = C\tilde{\rho}_0(t), \quad C = C(\theta) = \int_0^\infty d\tau e^{-iL_{cc}\tau} (-iL_{c0})e^{i\theta\tau} \quad (4)$$

The first Liouville equation (1) then yields a functional equation for θ :

$$\theta = L_{00} + L_{0c}C(\theta) \quad (5)$$

which can be solved by iteration.

The total asymptotic density $\rho = \rho_0 + \rho_c$ thus obtained has the remarkable property of being an exact solution of the Liouville equation. According to equation (4), it may be written in the form $\rho = P_a\rho$, with $P_a = P_0 + C$. It is again remarkable that this superoperator P_a has the characteristic properties of a projection operator in superspace, idempotency and "adjoint symmetry" (that is, it is such that the projection $P_a A$ of a self-adjoint supervector A is self-adjoint). The projector P_a defines a subspace in which the asymptotic density is confined. This subspace differs from the average subspace P_0 by the adjunction of a part of the correlation subspace P_c , namely that part which is specified by the super-

operator C ; the latter may be interpreted as representing the building up of correlations from asymptotic average situations (we call it the superoperator of correlation creation)—it sorts out those correlation processes which have a long time effect and accordingly manifest themselves at the macroscopic level. Thus, the asymptotic density $\tilde{\rho}$ is not, as one might have expected, governed by a “kinetic equation” different from the dynamical Liouville equation: it is an exact solution of the latter, and its asymptotic character is conferred upon it by its confinement to a subspace defined by the projector P_a .

The expression for the superoperator of correlation creation C , which enters in the definition of P_a , is clearly unsymmetrical in time, and gives the projector P_a the expected bias towards a preferred direction of the time evolution. In fact, time inversion transforms P_a into a different projector $\bar{P}_a = P_o + D$, where the superoperator

$$D = \int_0^\infty d\tau e^{i\eta\tau} (-iL_{oc}) e^{-iL_{cc}\tau}$$

is the time-inverse of C ; it contains the superoperator η which is the time-inverse of θ and obeys the equation $\eta = L_{oo} + DL_{co}$ derived from equation (5) by time-inversion. In contrast to C , the superoperator D describes sequences of “destructions” of correlations leading to asymptotic average situations.

An important element is still missing in the picture: we must establish a link between the asymptotic density supervector $\tilde{\rho}(t)$ and the arbitrarily chosen dynamical density supervector $\rho(o)$ from which the time-evolution is assumed to start. This is readily supplied, however, on the basis of a further remarkable property (easily derived) of the superoperator θ and its time-inverse η :

$$P_a\theta = LP_a, \quad \eta\bar{P}_a = \bar{P}_aL \quad (6)$$

With the notation $N_o = 1 + DC$, it follows from equations (6) and (3) that

$$N_o\tilde{\rho}_o(t) = N_o e^{-i\theta t} \tilde{\rho}_o(0) = e^{-i\eta t} N_o\tilde{\rho}_o(0)$$

and, on the other hand,

$$\bar{P}_a\rho(t) = \bar{P}_a e^{-iL t} \rho(0) = e^{-i\eta t} \bar{P}_a\rho(0)$$

This shows that $N_o\tilde{\rho}_o(t)$ and $\bar{P}_a\tilde{\rho}(t)$ have the same time-evolution, governed by the superoperator $\exp(-i\eta t)$: we may therefore equate them at any instant and in this way fix the correspondence between the dynamical and the asymptotic density. This gives the quite fundamental relation, valid at any time,

$$\tilde{\rho}(t) = \tilde{\Pi}\rho(t) \text{ with } \tilde{\Pi} = P_a N_o^{-1} \bar{P}_a \quad (7)$$

from which follows

$$\tilde{\rho}(t) = \tilde{\Sigma}(t)\rho(0) \text{ with } \tilde{\Sigma}(t) = \tilde{\Pi}e^{-iL t}$$

the answer to our last question, completing the theory.

The striking feature about the superoperator $\tilde{\Pi}$ occurring in equation (7) is that it is also a projector in the extended sense defined above (which does not include the property of self-adjointness); moreover, it is time-reversal invariant: it defines a time-symmetrical subspace of the superspace in which the asymptotic part of the time-evolution, starting from any given situation, remains confined, exhibiting the features observed at the macroscopic level; whereas the irregular fluctuations occurring on the atomic time scale are contained in the complementary subspace orthogonal to the asymptotic one. That such a clean separation between the two aspects of the atomic system could be effected is an entirely unexpected property specific to the density supervector representation: it could never have been found by a study of the evolution of the system in Hilbert space, for it can only be formulated in terms of the superspace formalism.

The superoperator $\tilde{\Pi}$ is not factorizable: one cannot ascribe any state vector to an asymptotic situation as we have defined it, but only a density supervector $\tilde{\rho}$. In fact, as appears from equation (4), the correlation part $\tilde{\rho}_c$ of the density ρ is directly derived from the part $\tilde{\rho}_o$ expressing the average probability distributions of the system; owing to this remarkable structure of the projector $\tilde{\Pi}$, the evolution in $\tilde{\Pi}$ -space may be entirely described in terms of probabilities only. In particular, the “reduction of the wave-packet” of an atomic system after its interaction with a measuring apparatus is a direct consequence of this property of the $\tilde{\Pi}$ -space description: the essential point being that the apparatus must necessarily belong to the macroscopic level of quantum mechanics, and that its behaviour must accordingly be described in terms of its $\tilde{\Pi}$ -space variables (loosely speaking, the behaviour of the apparatus has “thermodynamical” character, inasmuch as variables pertaining to thermodynamic equilibrium or near-equilibrium states all belong to $\tilde{\Pi}$ -space). Any phase relations in the initial state of the atomic system are therefore wiped out (that is, they are rejected into the orthogonal subspace): this is the only meaning of the “reduction” of the initial state of the atomic system resulting from the measurement. As to the human observer, his interaction with the apparatus is also entirely described in the $\tilde{\Pi}$ -subspace, and therefore without any influence whatsoever on whatever goes on in the orthogonal subspace.

One further point should be mentioned. The theory gives us a simple criterion to decide whether the system shows the normal macroscopic behaviour described by thermodynamics. The superoperator of asymptotic time-evolution θ is closely related to a “collision superoperator” defined as the Laplace transform of the superoperator $L_{oc}T_c(\tau)L_{co}$:

$$\Psi(z) = \int_0^\infty d\tau L_{oc}T_c(\tau)L_{co}e^{-z\tau}$$

Indeed, equation (5) may be written as a functional relation in terms of $\Psi(z)$:

$$i\theta = iL_{oo} + \Psi(-i\theta) \quad (8)$$

Now, an homogeneous system (a system for which $L_{oo} = 0$) will obviously not exhibit any tendency towards equilibrium if the collision operator vanishes identically. Equation (8) then shows that it will exhibit an irreversible tendency towards equilibrium provided that θ itself does not vanish identically. This “condition of dissipativity” is a practical one: it can be tested in concrete cases⁴ by actual computation of θ .

It is thus clear that the epistemological consistency problem raised at the beginning of this note is completely answered by the neat, clear-cut representation we obtain for the complementarity between the two levels of description of atomic phenomena. It need hardly be pointed out that the problem here discussed of the macroscopic level of quantum mechanics is just a simple illustration of a general method of representation in superspace, which actually amounts to an extension of the scope of quantum mechanics. Perhaps the most significant feature of the method is the introduction of generalized projectors, involving the replacement of self-adjointness by time-inversion invariance (which reduces to the former in the absence of dissipation, that is, for systems for which the collision operator vanishes)—a generalization which may be expected to find application to a large variety of problems.

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LETTERS TO NATURE

PHYSICAL SCIENCES

Computer Analyses of Gravitational Radiation Detector Coincidences

My earlier publications¹ have reported the concept, theory, and development of an antenna to detect gravitational radiation. These antennae are well isolated from the local environment by acoustic and electromagnetic shielding but they do respond to sufficiently large local disturbances. Effects of the local environments can, however, be minimized when two detectors are used which are a considerable distance apart. For this reason coincidence experiments at 1,661 Hz were carried out with two antennae, one situated at the University of Maryland and the other 1,000 km away at the Argonne National Laboratory.

For all experiments reported here the only coincidences which were recorded were those which occurred within a predetermined time Δt .

Coincidences may be due to excitation of both detectors by a common source or to chance. It is customary to compute the chance (accidental) coincidence rate by formulating a classification scheme for the coincidences and computing the number of chance coincidences in each class. A significant excess of detected event over the chance coincidence rate for a given class establishes with a certain level of confidence that not all coincidences are due to chance.

For two years the experiments were done as follows. The outputs of the Maryland and Argonne detectors are obtained from synchronous detectors which have free running crystal reference oscillators and twin channels with the reference shifted by $\pi/2$ in one of them. The two channel outputs are squared and summed to recover the power, with a time constant of 0.5 s. The envelope of the total power output of the Argonne detector was transmitted over a telephone line to Maryland, in coded digital form, and reconverted to analogue d.c. at Maryland. The outputs are fed to a coincidence detector. If both channels cross some preset threshold from below, within the time interval Δt , a pulse is emitted to drive a recorder marker pen.

The amplitudes of the noise pulses have a Rayleigh distribution, and their shapes vary widely. Analysis is simplified if all pulses have roughly the same shape, because then one parameter, the pulse height, will suffice for their classification. To shape the pulses properly a second stage of filtering is carried out after coincidence detection. There is a small amount of additional filtering associated with the mass of the pen which records the output on a chart.

A mean solar day is chosen as the unit of time. Consider a given coincidence with power amplitudes P_A and P_B for the two channels. Let N_A and N_B represent the number of times per day that the powers P_A and P_B are equalled or exceeded, on the average. Let Δt be the maximum time between threshold crossings for the two channels in order to record a coincidence. The expected number of chance coincidences with amplitudes equal to or exceeding those observed for an experiment with effective duration M days is η_{AB} with

$$\eta_{AB} = 2N_A N_B \Delta t M \quad (1)$$

To employ equation (1) we select some arbitrary numbers which may or may not be the same for channels A and B .

A given class consists of all those coincidences for which N_A and N_B each are equal to or less than the arbitrarily selected numbers for them.

A second classification scheme was employed in order to determine if the difference between the observed and chance coincidences is sensitive to details of the statistical methods. Instead of requiring N_A and N_B each to remain within certain bounds for a given class, we require the product $N_A N_B$ to be equal to or less than some arbitrary number for a given class. The total number of such chance coincidences will be finite because neither N_A nor N_B can ever be less than one or greater than the total number of pulses observed for each channel. The most useful classifications are those for which N_A and N_B are less than some number N_s which is about an order greater than the numbers which characterize most of the real coincidences classified by equation (1).

A two dimensional space with N_A and N_B as coordinates is useful to calculate the number of chance coincidences $\tilde{\eta}_{AB}$ for which the product $N_A N_B$ is equal to or smaller than some constant and for which neither N_A nor N_B exceeds some maximum value N_s . $\tilde{\eta}_{AB}$ is expression (1) plus the integral under the hyperbola $N_A N_B = \text{constant}$, that is

$$\tilde{\eta}_{AB} = 2N_A N_B \Delta t M [1 + \ln(N_s^2 / N_A N_B)] \quad (2)$$

In equations (1) and (2) M is smaller than the actual number of days which the experiments run, because allowance must be made for the detector relaxation time after crossing the threshold. A new coincidence cannot occur during this time.

Early experiments^{5,6} observed that the number of coincidences for certain values of N_A , N_B , $N_A N_B$ substantially exceeded the accidental rate computed from equations (1) and (2). These gave about the same numbers for the difference of the observed and chance coincidences. The conclusion that positive results are obtained is based on certain assumptions—for example that the classification scheme based on amplitude alone with the successive filtering is sound. To test this, a parallel experiment was done to measure the accidental rate by inserting time delays of varying length in one channel or the other.

This time delay experiment showed a large decrease in the number of coincidences for which N_A , $N_B \leq 100$; and also those coincidences for which $N_A N_B \leq 6,000$ with $N_s \leq 1,000$ for all time delays significantly larger than Δt . There is a subjective element in the data processing, in that for each coincidence mark the leading edge of the pulse must be examined. If it increases smoothly to a peak then the peak value is the required amplitude. If there is a discontinuity in slope before reaching the peak it is concluded that the excitation which results in a threshold crossing was followed at the discontinuity by a heat bath noise excitation. The required pulse height is then only the value measured to the point of discontinuity. Sometimes the discontinuity is not well defined and a human decision is needed.

Using a magnetic tape and a computer provides an independent procedure for data processing. The human element is only involved in the program preparation. A variety of thresholds and time delays can be applied to any stretch of data. The synchronous detector output with 0.5 s filter time constant was recorded in digital form every 0.1 s with both channels on one tape. A computer program was prepared by Mr Brian K. Reid in the following way: thresholds were set such that if both channels crossed from below within 0.5 s the computer measured the pulse heights after a second stage of 5 s time

constant filtering and a third stage of filtering with 0.5 s time constant to simulate the ink recorder pen. Then the computer counted the number of times the filtered data amplitude was equalled or exceeded for the previous hour, the previous 6 h, and the given day following the schematic diagram in Fig. 2. The same procedure was repeated for time delays of 1 s, 2 s, 5 s, 10 s, 20 s and 40 s.

The program was inaccurate beyond 20 s delay and the bin values given in Fig. 1 for 40 s delay are much too small. A subsequent computer program has verified that there is no further decrease in the chance coincidence rate for delays exceeding 100 times the coincidence window.

The pen and ink records show pulses with relatively smooth leading edges. The greater time resolution of magnetic tape results in pulses with a certain roughness everywhere. It is therefore difficult to prepare a program which measures the pulse height to a point of discontinuity in leading edge slope. The computer defines the peak as the point where a trend of increases is followed by a trend of decreases. Detailed study of greatly expanded pulses indicates that this is a sound procedure for most of the coincidences. Because of the 5 s averaging it is expected that the pulse peak will be reached between 2 and 15 s after the threshold is crossed and only those coincidences are recorded which reach peaks within such an interval. This range of values is required because of noise and the initial conditions of charge on the capacitors of the filter. The computer measures the area of the pulse, but this is not included in the statistical analysis.

A small fraction of the coincidences are not found by the program because no peak is found in the required interval following threshold crossing. Detailed plotting usually permits the peak to be identified within the required time after threshold crossing. Such coincidences are not included in these data in order to conserve computing time and costs.

Results are shown in Fig. 1 for all coincidences for which $N_A N_B \leq 10,000$ and $N_S \leq 1,000$. The low intensity coincidences are often counted more than once if threshold is crossed and re-crossed in the presence of noise. The histogram therefore shows about twice the real number of coincidences for the 120 day period covered by the tapes. All data of Fig. 1 came from the computer and not from human examination of printed lists.

It is significant that for delays in either channel as small as twice the coincidence interval Δt , the coincidence rate drops by a factor about 2.5. At delays of 20 s the coincidence rate is down by roughly a factor 10. These data, untouched by human hands, leave no doubt whatsoever that the gravitational radiation detectors, separated by 1,000 km, are being excited by a common source.

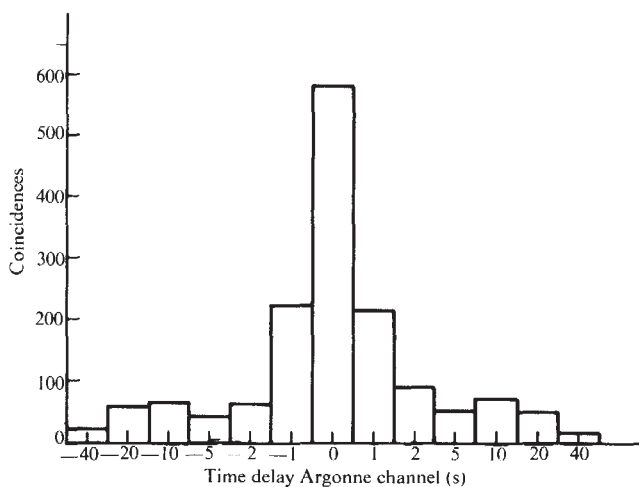


Fig. 1 Computer analyses of magnetic tapes, October 1970–February 1971.

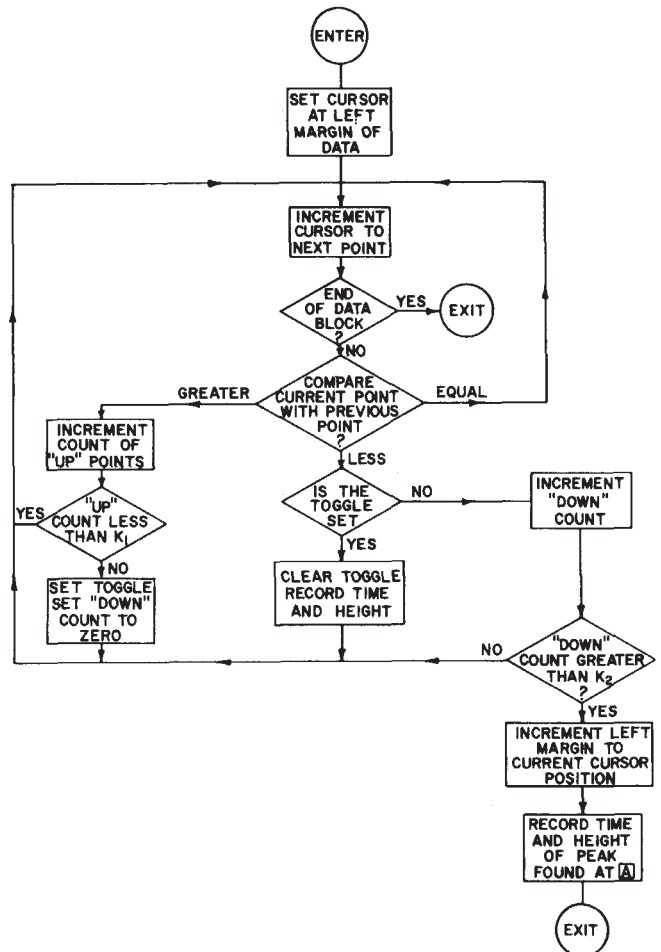


Fig. 2 Computer program for statistics of coincidences recorded on magnetic tape.

Before we can conclude from Fig. 1 that the source is gravitational radiation, it is essential to rule out other presently known interactions including seismic, electromagnetic, and cosmic ray effects.

The detectors are coupled to each other by the Earth and respond to sufficiently large seismic events. A number of seismometers were developed including a vertical axis accelerometer tuned to the detector frequency of 1,661 Hz, a three axis accelerometer covering frequencies near 100 Hz, and a two axis tilt meter. No significant correlations were observed between seismic activity and the coincidences.

Electromagnetic signals may enter the instrumentation through the vacuum chambers and through the cables and shields of the electronic equipment. Experiments were carried out to measure the susceptibility to electromagnetic excitation. It was found that 1,661 Hz magnetic fields of amplitude about 0.1 Gauss will excite the detector, and much larger fields at 830.5 Hz will also excite the detector. Non-linear effects are expected because the electromagnetic stress tensor is quadratic in the fields, and electromagnetic stresses can cause mechanical forces on the detector cylinders. The response is large at 1,661 Hz because the electronics has its acceptance band there and because 1,661 Hz currents in the aluminium cylinder give forces by interacting with the Earth's magnetic field.

Both laboratory sites are to some degree shielded as a result of grounded metal ceilings and structures around the apparatus. A radio receiver was employed at the Maryland site, with non-linear pre-amplifier and post-amplifier tuned to a narrow band of frequencies near 1,661 Hz. The receiver sensitivity could be adjusted to respond to fields much smaller than those which excite the gravitational radiation detectors.

Magnetic and electric dipole antennae were employed at different locations and with different orientations at various times. Local electromagnetic fields associated with air conditioning, magnetic tape recorders, and power line fluctuations limited the radio receiver sensitivity to values about three orders smaller than those to which the gravitational radiation detector responds. No significant correlations were observed with the gravitational radiation detector coincidences.

There is additional evidence that the coincidences are not due to electromagnetic or seismic interactions. The gravitational radiation detector system input temperature has been measured by a noise generator. This resulted in an accurate accounting of all significant signal sources and ruled out the possibility that any significant fraction of the input temperature is due to some background other than internal noise. If the coincidences are caused by terrestrial effects such as seismic and electromagnetic activity, these must give signals arriving simultaneously or nearly simultaneously at both sites from a region on or within the Earth. For each coincident arrival at the two locations, however, there must be many individual arrivals, and these would result in a higher system noise level than is observed. Measurements were also carried out of coincidence rates for a pair of gravitational radiation detectors at the Maryland site over a period of six months. Within limits of experimental error the one-site, two-detector coincidence rate was identical with the separated-site two-detector coincidence rate. This indicates that for the sensitivities reported here, the isolation from the local environments was adequate and that electromagnetic and seismic interactions do not cause the observed coincidences.

The separation of 1,000 km makes a cosmic ray shower explanation very unlikely. Nonetheless it was important to investigate the effect of cosmic ray charged particles. Professors N. Sanders Wall and Gaurang B. Yodh and Dr David Ezrow instrumented one of the Maryland site gravitational radiation detectors with Čerenkov radiation counters and later with meter square plastic scintillators. They observed no significant correlations with the gravitational radiation detector coincidences⁷.

A search was made for coincidences between a 1,661 Hz gravitational radiation detector and a 5,000 Hz mode of a second gravitational radiation detector, both at the Maryland site. No excess of coincidences above the chance rate was observed. Subsequent investigation showed that the 5,000 Hz mode was a bending mode and not a compressional mode. General relativity theory predicts that this bending mode should not interact with gravitational radiation. The lack of coincidences is thus evidence against a non-gravitational radiation origin for the 1,661 Hz coincidences.

Other papers have presented evidence that there is anisotropy of the observed coincidences, the maxima occurring in the direction of the galactic centre⁸. Experiments with a disk were consistent with predictions of Einstein's pure tensor theory. Small effects of the local environment can affect the anisotropy in a significant way. To average these properly at least six months of data are required. The magnetic tapes considered here did not have times continuously written. Gaps and recorder failures left insufficient data for a study of the anisotropy. Visual examination of the lists of coincidences found by the computer implied that the data are consistent with the earlier anisotropy experiments based on human observer study of pen and ink recorder charts.

The present data are free of human observer bias. No assumptions are made concerning the duration of expected pulses or their shapes beyond the requirement of a fairly smooth leading edge. This is important because addition of noise will change the shape of received pulses. It is considered established beyond reasonable doubt that the gravitational radiation detectors at ends of a 1,000 km baseline are being excited by a common source as a result of interactions which are neither seismic, electromagnetic nor those of charged particles of cosmic rays.

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Atmospheric Gravity Waves to be Expected from the Solar Eclipse of June 30, 1973

Chimonas and Hines¹ have pointed out that the Moon's shadow on the Earth's atmosphere during a solar eclipse constitutes a cooling region travelling at supersonic speed.

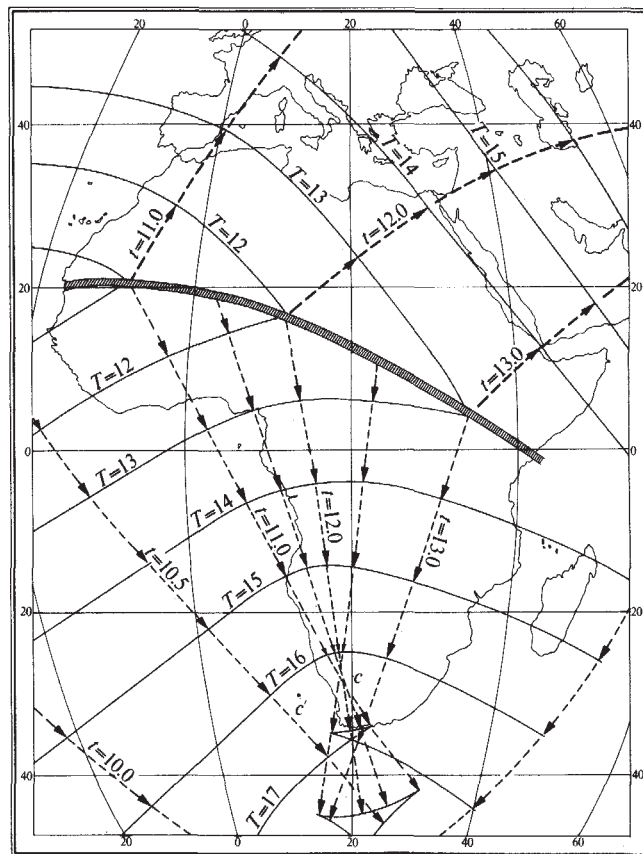
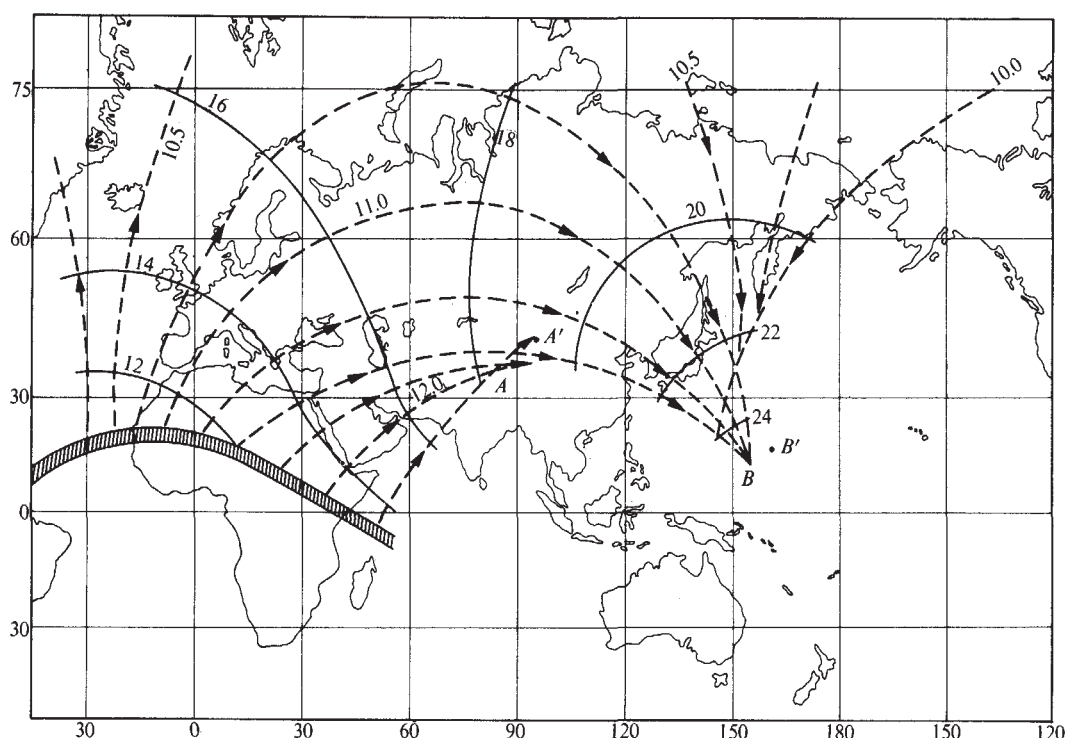


Fig. 1 Focusing of south going bow waves. The wave fronts (continuous) are drawn at 1 h intervals of T , and the wave normals at 0.5 h intervals of t . The value of C_1 is taken to be $10.3^\circ \text{ h}^{-1}$. When a value of 7.8° h^{-1} is adopted the focus at C shifts to C' .

Fig. 2 Focusing of north going bow waves (Mercator projection). The wave fronts are at 2 h intervals, and the wave normals at 0.25 h intervals. Again C_L is taken as $10.3^\circ \text{ h}^{-1}$. For 7.8° h^{-1} the foci shift from *A* and *B* to *A'* and *B'*.



It may therefore be expected to generate a bow wave with a magnitude of about 10^{-5} atmosphere at ground level and 10^{-1} of ambient pressure at 200 km altitude. Chimonas² estimates the frequency of the bow wave to be very low, corresponding to a period of about 4 h.

Observations of ionospheric disturbances during the eclipse of March 7, 1970, revealed³⁻⁵ a period of the fluctuations of 20 min rather than the 4 h predicted. Chimonas and Hines⁶ ascribe the discrepancy in the period to the fact that the observations were made at points relatively close to the eclipse path, at the edge of the penumbra. In such cases disturbances originating at points in the penumbra close to the point of observation can predominate over the fully developed bow wave in which the effect of the whole shadow region is combined. There seems little reason to doubt that the ionospheric disturbances reported were in fact due to the eclipse. There are no reports of microbarograph effects at ground level from the eclipse of 1970 or indeed from any other eclipse.

The solar eclipse of June 30, 1973, will provide another opportunity of investigating these effects. We have made calculations of the form of the bow wave to be expected and in particular of the positions and times at which focusing effects could be expected using the eclipse path calculated by Duncombe⁷.

Inspection of the eclipse path suggests that focusing due to the curvature of the path will occur near 18° S , 18° E . For a fixed value of C_L , the velocity of propagation of the bow wave, the angle θ between the bow wave front and the eclipse path is given by $\sin \theta = C_L/V$ where V is the velocity of the eclipse shadow. The direction of the eclipse path and the value of V were determined numerically from the values given by Duncombe⁷. From these the direction of the north and south going wave normals can be determined. The wave normals proceed along great circles as described by Fermat's theorem of least time; thus the position of the disturbance originating at any time t can be found at any subsequent time T . The final result of the calculation is a series of values of the latitude and longitude of the disturbance as functions of t and T . When these are plotted for constant values of t they give the wave normals, and plots of constant T give the wave fronts (Figs. 1 and 2).

The calculations were carried out for two values of C_L , $10.3^\circ \text{ h}^{-1}$ (320 m s^{-1}) and 7.8° h^{-1} (290 m s^{-1}). It seems

likely that actual values for the propagation velocity of long period gravity waves would be between these values. The results are not very sensitive to the value of C_L .

Table 1 Positions and Times of Occurrence of Foci

	$C_L = 7.8^\circ \text{ h}^{-1}$			$C_L = 10.3^\circ \text{ h}^{-1}$		
	Latitude	Longitude	T	Latitude	Longitude	T
North going waves	43° N	95° E	21.5 UT	37° N	86.5° E	18.5 UT <i>A</i>
	15.5° N	161° E	29 UT*	12.5° N	154° E	25 UT* <i>B</i>
South going waves	30.5° S	12.5° E	18 UT	26° S	17.5° E	16 UT <i>C</i>

* Equivalent to 5 h and 1 h respectively on July 1.

Three well marked foci appear in the plots. The positions and values of T for these are shown in Table 1. Focus (*A*) is over Tibet. It is formed by disturbances originating between 11.5 h and 13 h and is due to the acceleration of the shadow at the end of the path. Because the waves arriving at this focus come from only a short portion of the path and converge at a small angle this focus will be weak and diffuse. Focus (*B*) is formed by waves originating between 10 and 11.5 h. This is the central part of the eclipse path, the focus is likely to be rather strong and since the waves converge over a large angle ($\sim 60^\circ$) it is likely to be comparatively well defined. Focus (*C*), in southern Africa, is the principal focus of south going waves, but it is located on the edge of the penumbra. The effects there are likely to be of the same kind as those observed over California in the 1970 eclipse.

This discussion is over-simplified in several respects. First, the eclipse path is treated as a curve line following the path of totality—in other words the effects arising from the penumbra are ignored. This is probably a good approximation for the distant foci (*A*) and (*B*) but not for (*C*). Second, the problem is treated as in geometrical optics. Diffraction effects will make the foci much more diffuse than appears in Figs. 1 and 2. Thus if the period of the disturbance is as long as 4 h the corresponding wavelengths will be about 4,000 km. Even for a wide angle of convergence such as in the Pacific focus (*B*) the diameter of the diffraction pattern will be of this order. Finally, the propagation of the bow wave has been assumed to be

along great circles at constant speed. All complications due to the structure of the atmosphere have been ignored.

The observation of ionospheric and ground level microbarograph disturbances would clearly be of the greatest interest.

We would also like to draw attention to the possibility that the daily heating and cooling at sunrise and sunset could give rise to effects of this kind. The terminator moves at supersonic speeds between $\pm 45^\circ$ latitude at all altitudes below 100 km. This is liable to produce a continuous daily spectrum of gravity waves and could provide an important source for the gravity waves observed in the ionosphere under normal conditions.

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Neutral Wind Measurement during Daytime in the Thermosphere

A SKYLARK rocket (SL 1023) was launched in the British National Space Research Programme at Woomera Range, S. Australia, at 1130 local time on March 14, 1972. The objective was to make a detailed analysis of the structure of the local daytime ionospheric current system. The study included measurements of vertical profiles of electron density and temperature, electric field, vector magnetic field and neutral wind velocity between 90 and 260 km (vehicle apogee). A detailed report of these measurements will be made at a later date.

Here we discuss only one experiment; the measurement of neutral wind velocity during daytime, above 90 km altitude, using ground-based optical observations of a lithium and sodium vapour trail released from a rocket.

The feasibility of daytime measurement of neutral wind above 100 km was demonstrated by Bedinger¹ who observed a lithium trail from a dawn twilight experiment until about 30 min after local sunrise from a single observation site,

using a differential photometer. In further trials Best² also tracked a dawn experiment into daylight and later (personal communication) successfully observed a lithium point cloud released near 200 km altitude by a rocket launched at midday, again using a differential photometer.

Bedinger³, during a dawn twilight experiment, successfully photographed directly through a narrow bandpass interference filter a lithium cloud until just after local sunrise, from an aircraft at an altitude of 12 km. At such an altitude the intensity of the daytime sky is much lower than at ground level and, theoretically, photographs from a single moving observation site such as an aircraft can be deconvolved by a computer to obtain neutral wind speed. This analysis has not yet been demonstrated and, as in the case of previous single ground station observations, may result in a lower accuracy wind determination.

During the Skylark experiment a lithium trail was released on the downleg of the rocket trajectory between about 205 and 160 km. The cloud was successfully observed from three ground-level sites and tracked for a period of about 30 min. The detailed design of the instruments used and their recording and monitoring facilities will be discussed elsewhere and only the most general features described here.

Narrow bandpass differential photometers were operated at both the C19 and B5 sites (Fig. 1). The principle of operation was similar to that used by both Bedinger and Best; a beam splitter passed geometrically identical beams through two narrow bandpass (0.25 nm) interference filters, one tuned to the lithium wavelength (670.78 nm) and the other detuned between 0.3 and 0.4 nm from this wavelength. Both instruments operated successfully.

A 25 mm diameter solid Fabry-Perot plate, resolution 0.01 nm, free spectral range 1 nm, was used in series with a 0.3 nm narrow band interference filter, and the combination tuned to the lithium wavelength. The intensity of a clear daytime sky, within the 0.01 nm bandwidth, is less than that of a sunlit lithium cloud in the upper atmosphere, so that there is no need to use a comparator to detect the cloud. The instrument recorded the lithium cloud for a period of about 20 min from the B7 site (Fig. 1), comparable with the two differential photometers.

The third technique used the resonance properties of sodium vapour in an optical cell at about 422 K in the focal plane of a camera lens, as a selective filter to attempt to observe the sunlit cloud of sodium vapour released from the rocket. In theory only that light within the thermal bandwidth of the vapour in the cell, which is rather narrower than the bandwidth of the sodium "D" lines at model temperatures above 120 km (400–900 K), should be resonantly scattered. The detection and recording system used a high gain image intensifier to enhance the resonantly scattered image and a Hasselblad

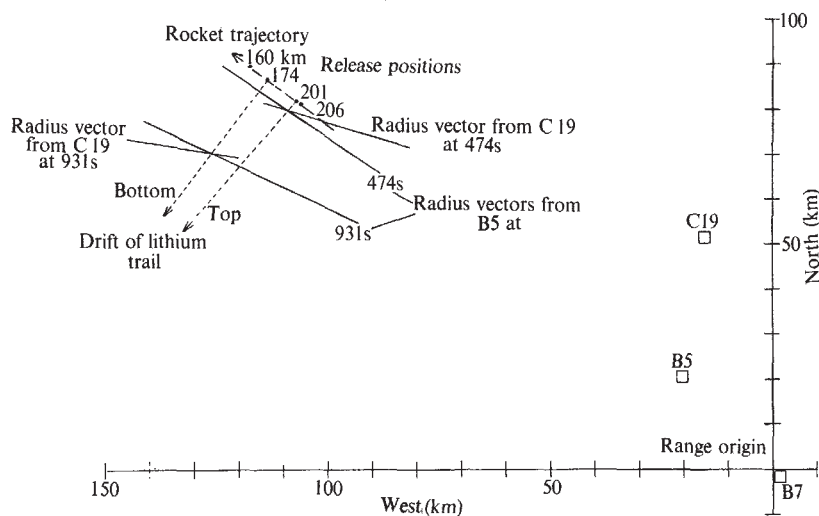


Fig. 1 Radar rocket trajectory and drifts of top and bottom of lithium trail projected on to a horizontal plane.

single lens reflex camera to record and monitor the field of view.

No positive records were obtained during the trial, although visually it appeared that a cloud could have been detected for a short period soon after the start of the trail release. During trials before the experiment, however, the instrument performance was comparable with that of the photometer systems and the instrument should be capable of observing a daytime sodium cloud. If technical difficulties of using lithium in the vapour cell arising from the necessity for a much higher temperature than for sodium (350–400° C compared with 150° C) could be overcome, the instrument would have appreciable operating advantages over the photometer systems.

To analyse the drift of the lithium clouds, an accurate knowledge of the azimuth and elevation of the direction of viewing is required. Photometers were mounted on calibrated horizontal optical tables and scanning of the field of view was achieved by plane mirrors, mounted before the objectives of the photometers. Data obtained at B7 and C19 were recorded on a digital cassette tape recorder. Time code, instrument output, azimuth, elevation and word markers were all digitally multiplexed into a 60-bit frame, scanned at 80 Hz.

The thermite burn commenced at 370 s after launch at 206 km altitude on the downleg of the rocket trajectory and, unfortunately, only lasted for about 10 s instead of a planned 100 s. For at least another 20 s, however, to below about 160 km altitude, the hot container outgassed enough lithium vapour to produce an observable trail about 45 km long. Between 50 s after release (420 s after launch) and about 1,200 s after launch all three sites successfully tracked this trail. Acquisition of the trail and the later data reduction were greatly facilitated by liaison immediately after launch with the radar team, which enabled a correction to be made to the azimuth of all instruments to compensate for a 12° deviation of the rocket from the planned trajectory azimuth. The radar trajectory and the monitor of trail emission given by on-board instrumentation enabled a very accurate recalibration of the scanning instruments, so that error residuals throughout the observations were reduced to the order of 0.2° in both azimuth and elevation, comparable with normal night-time and twilight photography of chemical releases near 200 km, by conventional star plate analysis.

Fig. 1 shows a simplified schematic of the observation sites, range origin, reduced radar trajectory and the directions of movement of the top and bottom of the trail as seen from both B5 and C19 sites, all projected on to a horizontal plane. The drift of the trail between 474 and 931 s after launch is taken from a best linear fit to eight images of the trail from B5 site over 970 s and ten from C19 site over a period of 517 s.

The neutral wind velocities reduced from the preliminary analysis are given in Table 1.

Table 1 Neutral Wind Measurements from SL 1023

Altitude (km)	Velocity (m s ⁻¹)	Azimuth (° clockwise from N)
202	32 ± 2	221 ± 2
176	35 ± 2	219 ± 2

The wind velocities between 202 and 176 km were rather lower than the median of twilight wind observations (about 80 m s⁻¹) reported recently by Lloyd *et al.*⁴. The wind shear was also rather low, about 10⁻⁴ s⁻¹, compared with values reported at twilight between 170 and 200 km of about 10⁻³ s⁻¹ (refs. 4 and 5). Both a low vertical shear and low wind speed could be expected if ion drag damping in the F region dominated neutral gas movement during the daytime. Cho and Yeh⁶ have calculated for an equinox, medium solar activity situation, a velocity, accounting for ion drag and using a Jacchia 1965⁸ model atmosphere, of 60 m s⁻¹ at about 225°

for the local time of the launch, corrected to the southern hemisphere, comparable with our result.

The project was supported by the British Science Research Council. The integrated payload was prepared by the Space Science and Atmospheric Structure Research Group and the Mullard Space Science Laboratory, University College London, and the Department of Space Research, University of Birmingham. The rocket firing at Woomera Rocket Range was supported jointly by BDRSS and WRE Ranges Group, Weapons Research Establishment of the Australian Department of Supply. Support for optical ground equipment has been provided by the Science Research Council.

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Pressure-induced Reduction of a Ferric Amphibole

Most ferric salts and complexes undergo reversible reduction at high pressures^{1,2}. These results have important implications in geochemical studies of the mantle³ and suggest that ferric-bearing silicates might be reduced to the ferrous state at high pressures. We report here results of Mössbauer measurements at high pressures on a synthetic ferric amphibole, which is a possible component in the Upper Mantle. The data indicate that Fe³⁺ ions may be reduced to Fe²⁺ ions in minerals of the Earth's interior.

Amphiboles, which are hydroxyl-bearing double-chain silicates, are important constituents of the crust^{4,5}. They occur not only in a variety of igneous and metamorphic rocks that crystallized at moderate temperatures and pressures, but also in alkali amphiboles such as Na₂(Mg,Fe²⁺)₃(Al,Fe³⁺)₃Si₈O₂₂(OH)₂, which are ubiquitous phases in glaucophane schists that formed at high pressures in regions of tectonic activity^{6,7}. Pargasitic amphiboles, (Ca,Na,K)₂₋₃(Mg,Fe²⁺,Al,Fe³⁺,Ti)₅(Si,Al)₈O₂₂(OH)₂, containing significant amounts of Fe³⁺ ions, are postulated to occur in the Upper Mantle⁸⁻¹². The data reported here are for magnesioriebeckite, Na₂(Mg,Fe²⁺)₃Fe³⁺₃Si₈O₂₂(OH)₂, which was synthesized hydrothermally from a finely powdered oxide mix at a temperature of 800 ± 2° C and a pressure of 1 kbar under conditions close to those of the Ni/NiO buffer¹³. The Fe₂O₃ used in the synthesis

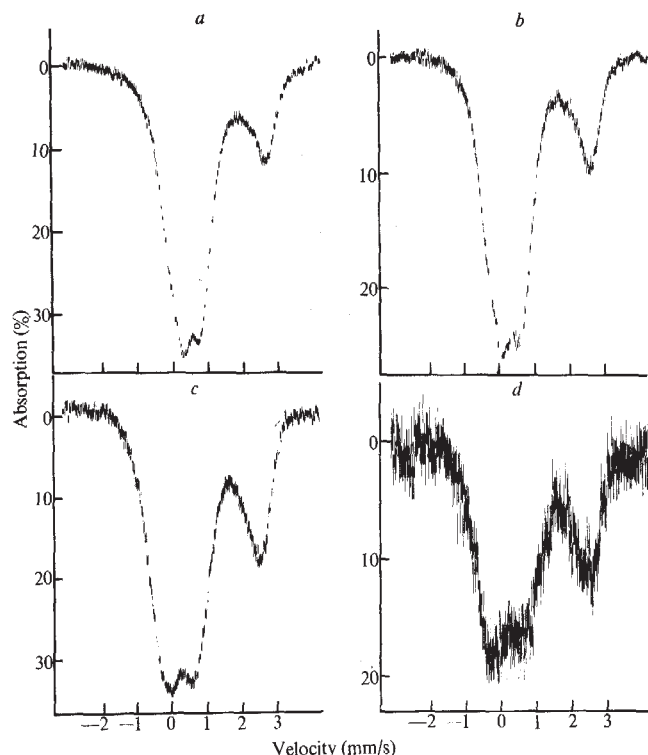


Fig. 1 Mössbauer spectra of magnesioriebeckite. *a*, Powder at 1 atm; *b*, pellet at 1 atm; *c*, pellet at 20 kbar; *d*, pellet at 57 kbar.

contained iron with >90% of the Mössbauer active isotope ^{57}Fe . The conditions of the synthesis, therefore, were within the experimentally determined stability field of magnesioriebeckite¹⁴. The purity of the synthetic product was verified optically and by X-ray diffraction.

Room temperature, atmospheric pressure spectra were measured first on the powdered synthetic ^{57}Fe -enriched amphibole. The powdered sample was held in a plastic annulus in a geometric configuration identical to that used later for the sample pellets. The spectrum illustrated in Fig. 1*a* indicates that about 33% of the iron is present initially as Fe^{2+} in the sample subsequently used in the high pressure studies. The spectra were fitted to six peaks (Fig. 2) consisting of two ferrous and one ferric doublet. The outer and inner doublets represent Fe^{2+} ions in the amphibole M1 and M3 sites, respectively, while the most intense peaks represent octahedrally coordinated Fe^{3+} ions^{15,16}. Previous work has shown that negligible amounts of Fe^{2+} ions occupy the smaller M2 positions which are favoured by Fe^{3+} ions in alkali amphiboles^{17,18}, whereas small amounts of Fe^{3+} ions are distributed over the M1 and M3 positions¹⁹.

The high pressure Mössbauer measurements were made with an assembly designed by Debrunner *et al.*²⁰. Sample pellets were prepared using a 1 mg mix containing the amphibole diluted with boron in a ratio of 1:8. This produced a pellet, diameter 0.53 mm, thickness 0.38 mm, which was enclosed in a boron/lithium hydride annulus. The complete pellet, including the annulus, had been compacted under a pressure of approximately 18 kbar. The pressure was determined using an approximate calibration based on the shift of the X-ray diffraction peaks of aluminium powder in an identically prepared pellet²¹. The Mössbauer spectrum of a pellet in the Drickamer cell at one atmosphere (Fig. 1*b*) shows a significant increase in intensity of the peaks attributed to Fe^{2+} ions over the powdered sample (Fig. 1*a*) which we attribute to locked-in strain^{1,2}. But there is close agreement in the isomer shift and quadrupole splitting parameters derived from the Mössbauer spectra of powdered and pelletized samples at one atmosphere (Fig. 4).

The high pressure spectra of the pellet show an increasing proportion of Fe^{2+} ions (Fig. 1*c* and *d*), indicating that appreciable amounts of Fe^{3+} ions are reduced. Beyond about 20 kbar there is a pronounced drop in the production of Fe^{2+} ions (Fig. 3), suggesting that Fe^{3+} ions in certain sites are more susceptible to pressure-induced reduction than others. Preliminary measurements on the synthetic ferric pyroxene acmite, $\text{NaFeSi}_2\text{O}_6$, indicate that small or insignificant reduction of Fe^{3+} ions in the pyroxene structure occurs over the same pressure range.

The variations of isomer shift and quadrupole splitting of each iron cation are shown in Fig. 4. The isomer shift of Fe^{2+} in the M1 positions and of Fe^{3+} ions concentrated in M2 positions show small but distinct decreases with rising pressure. This trend is in agreement with previous measurements of iron salts^{1,2}. There is a dramatic increase in isomer shift for Fe^{2+} ions located in the M3 site over the pressure range 1 atm–20 kbar which could be caused by a change in the charge balance of surrounding ligands resulting from the reduction of iron. The M3 site also shows a large relative increase in the percentage of Fe^{2+} with pressure (Fig. 3). In addition, marked diminution in the quadrupole splitting of Fe^{2+} ions in the M3 site takes place over this pressure range, whereas the Fe^{2+} (M1 site) and Fe^{3+} ions show a small increase (Fig. 4).

The preferential reduction of Fe^{3+} ions in specific sites may

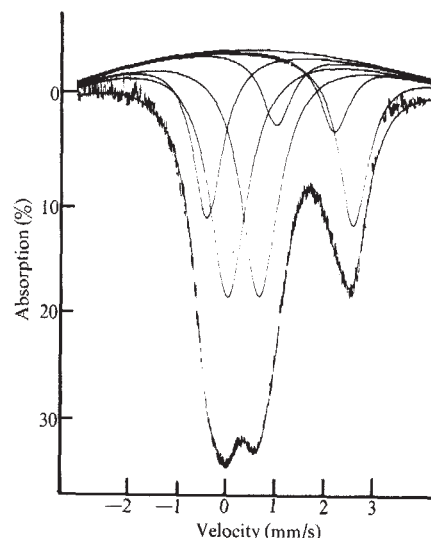


Fig. 2 Fitted Mössbauer spectrum of pellet at 20 kbar.

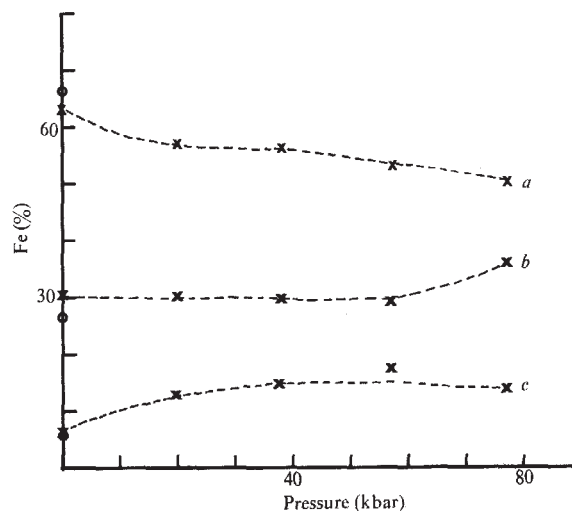


Fig. 3 Percentage Fe versus pressure (kbar) for three iron cations in magnesioriebeckite. *a*, Fe^{3+} , M2; *b*, Fe^{2+} , M1; *c*, Fe^{2+} , M3.

be interpreted as follows. Cations in the M1 and M3 positions of the amphibole structure are coordinated to four oxygen ions which are bound to silicon atoms of the linked tetrahedra, and to two free OH⁻ ions in the O3 positions²². These are in *trans* configuration in the M3 site and in the *cis* arrangement in the M1 site. The smaller M2 site, on the other hand, consists of six oxygen ions each bound to silicon atoms. We interpret the Mössbauer spectra of magnesioriebeckite at high pressure as indicating preferential reduction of the Fe³⁺ ions located in the M1 and M3 positions, the mechanism of which may be facilitated by the oxidation of OH⁻ ions to OH free radicals. The absence of free OH⁻ ions about the M2 positions renders pressure-induced reduction of Fe³⁺ ions in this site more difficult. This interpretation is supported by the negligible reduction of Fe³⁺ ions observed in acmite. In the pyroxene structure, Fe³⁺ ions occupy M1 positions which are analogous to M2 positions in amphiboles and contain no OH⁻ ions²².

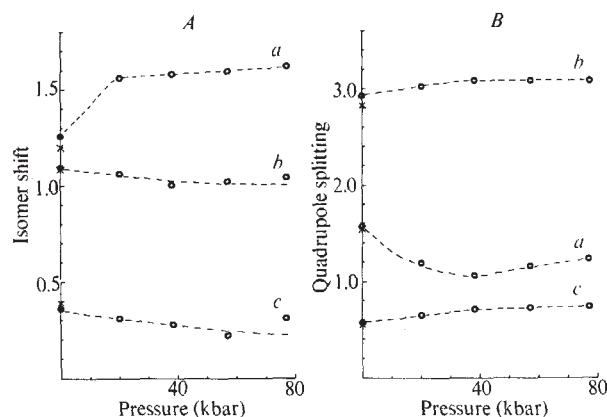


Fig. 4 Mössbauer parameters for magnesioriebeckite. A, Isomer shift versus pressure; B, quadrupole splitting versus pressure. Calibration relative to iron-foil standard. a, Fe²⁺, M3; b, Fe²⁺, M1; c, Fe³⁺, M2.

Ernst⁷ has suggested that glaucophane schist facies rocks crystallized during movement of lithospheric slabs down subduction zones into a high pressure but relatively low temperature environment. The characteristic glaucophane schist mineralogy was retained by uplift of these metamorphic rocks to shallower depths prior to the establishment of a normal geothermal regime. Analyses of the alkali amphiboles from such rocks frequently contain a deficiency of alkali metal cations²³⁻²⁵, possibly due to the coupled substitution of OH groups in O3 positions and Fe²⁺ ions in the M1 and M3 positions, which would require fewer Na⁺ ions to maintain charge balance. Release of pressure upon uplift would generate the small amounts of Fe³⁺ ions detected in the M1 and M3 positions¹⁹ of alkali amphiboles.

Ferric ions are postulated to occur in the mantle. Estimates of the Fe³⁺/total Fe ratio range from about 5% for the pyrolite model²⁶ to more than 18% for the volatile rich portions that may occur beneath mid-oceanic ridges²⁷. The stability fields of pargasitic amphiboles are such⁸⁻¹² that these hydroxyl-bearing phases could accommodate most of the iron in the Upper Mantle. Our results for magnesioriebeckite indicate that a large proportion of the Fe³⁺ ions are reduced to Fe²⁺ ions in the amphibole structure at the high pressure found in the Upper Mantle. Moreover, these observations, together with those derived from studies of ferric salts^{1,2}, lead us to postulate that low valence cations such as Fe²⁺, Cr²⁺ and Ti³⁺ may predominate in the Lower Mantle.

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Nitrogen Hydride as a Possible Stratospheric Constituent

THERE is considerable interest at present in the photochemistry of the stratosphere because of fears that future pollution at high levels, for example by supersonic aircraft, may change the stratospheric ozone. The ozone shields us from solar ultraviolet radiations and life seems to be delicately adjusted to its presence. The possible influence of nitrogen compounds is the subject of special study but in no case is there yet any information about their distribution in the stratosphere and their photochemistry is in great doubt; the quantities involved are certainly very small.

As part of a programme to improve spectroscopic photometric methods of measuring ozone we have made a precision spectrophotometer which measures, essentially simultaneously, the intensities of four wavelengths. The wavelengths chosen were 3104, 3171, 3242 and 3317 Å. Slit widths correspond to about 2 Å. During an extensive series of trial measurements made at Toronto, Ontario (43° N 79° W), persistent slight inconsistencies were observed. Further, when the instrument was taken to Kingston, Jamaica (18° N 77° W), to take advantage of the smaller and more steady ozone levels of the tropics, the inconsistencies increased and became clearer so that we

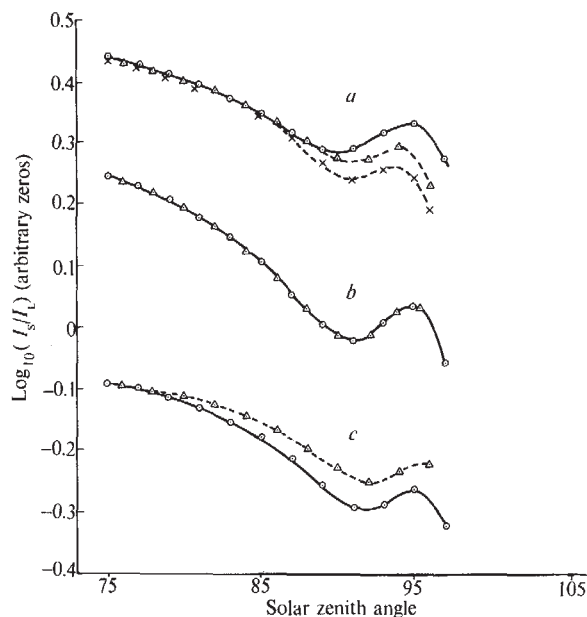


Fig. 1 Observed and expected values of $\log_{10}(I_s/I_L)$ against solar zenith angle. $\odot$, Calculated score only; $\triangle$, observed (Toronto); $\times$, observed (Jamaica). a, 3242 Å, 3317 Å; b, 3253 Å, 3328 Å; c, 3285 Å, 3360 Å.

could show that there must be a layer of some substance between 40 and 50 km height which absorbed at 3242 Å.

In private discussions, R. W. Nicholls suggested NH as a possible identification because 3242 is probably the (O, O) band of $c^4\Pi-a^1\Delta$ (λ , 3240) (ref. 1), which is due to NH in an excited metastable state, and he also suggested that we investigate 3360 Å where NH has further absorption in its ground state (O, O) band ($A^3\Pi-X^3\Pi$) (refs. 2-4).

Preliminary observations made by shifting our wavelengths by 43 Å (to 3147, 3214, 3285 and 3360 Å) show that there is similar absorption at 3360 Å. In a control experiment in which our wavelengths were moved by 11 Å (to 3115, 3182, 3253 and 3328 Å) we find we avoid inconsistencies of the type which occur at 3242 and 3350 Å. NH has a single line at 3253 Å which would not be expected to produce observable effects. This seems to us to suggest that there is indeed a layer of NH which at sunset is at 40 to 50 km. Examination of our measurements suggests the following features.

First, the amount of absorber has some diurnal variations. It is probably about an order of magnitude greater when the Sun is overhead than at sunset. Second, when the Sun is high at Toronto the optical absorption for vertical transmission at 3242 Å is about 1%. It is about 2% at 3360 Å and about 2% at 3242 Å at Jamaica. Third, at sunrise and sunset the material which absorbs at 3242 Å is in the layer 40 to 50 km at both Toronto and Jamaica. We cannot measure the height at other times. The similarity between sunrise and sunset and the larger amounts at noon suggest a photochemical equilibrium condition for excited NH with a relaxation time of the order of minutes or less. Fourth, at dawn, ground state NH, which absorbs at 3360 Å, appears to be small in amount and at 40 to 50 km but at sunset is much larger in amount and is in a deeper layer from 30 to 50 km.

The effects are most clearly seen in measurements of the zenith sky at sunrise or sunset; Fig. 1 is a diagram of the observed and expected march of the value of $\log_{10}(I_s/I_L)$ against solar zenith angles which shows the disagreements. These departures, following the well known Umkehr technique⁵, identify the height of the layer fairly closely.

It seems that the absorber is produced by photochemical effects but from what precursor or by what radiation we cannot say. Nitrogen hydride is produced in the laboratory by photolysis of hydrazine NH_3 , isocyanic acid vapour $HCNO$ (ref. 4), and in other ways. At sunset the optical depth of the

40 to 50 km layer ($\rho \approx 2$ mbar) is approximately equivalent to that of the 45 to 50 mbar layer with the Sun overhead. Only radiations with wavelengths between 0.19 and 0.22 μm or with wavelengths longer than 0.33 μm penetrate in significant quantities to this depth. Only these radiations can be involved.

We cannot guess the quantity of absorber involved. We can find no published date of line strengths of NH. Its optical properties are apparently very intense since it is not detectable by mass spectrometry in a discharge, even when its optical spectrum is very obvious⁶.

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Lower Limit and Maximum Age for the Last Major Advance of the Carstenz Glaciers, West Irian

ACTIVITIES of the recent Australian Universities Carstenz Glaciers Expedition included a search for the lowest morainic material in the East Otomona Valley. The presence of till there was first recognized by Dozy¹ in 1936 during an expedition from the south coast to the Carstenz Toppen (rendered Carstenz on Indonesian maps). Dozy reported finding morainic material overlying old river gravels, the lowest glacial deposits being between 1,900 m.y. and 2,200 m.y. This is lower than has been recorded for former glaciers in other tropical areas to date (for example, the east side of Mt Ruwenzori, 2,000 m; ref. 2), and Verstappen³ has queried whether post-glacial river transport of the morainic material to lower altitudes has not occurred.

Mining operations and access road construction between the south coast and the Ertsberg ore body at the head of the East Otomona Valley at 3,600 m have resulted in accurate height data and extensive excavations. These have allowed a re-examination of the areal and altitudinal extents of the glacial deposits mapped by Dozy¹ and a search for datable organic matter in the till. A timed altimetric traverse using paired Thommen microbarometer altimeters between bench marks at 2,402 m and 1,996 m over a period of 11.5 h, with temperature and humidity corrections applied, showed that the lowest glacial deposit investigated was at an altitude of 1,705 m above sea level.

The base of this deposit (Fig. 1), an *in situ* till, contained several broken, medium sized, logs of wood, one of which we collected for radiocarbon assay. The sample was divided by extraction with hot 2% NaOH; the residue gave a radiocarbon age of $10,000 \pm 130$ yr BP (SUA 28A). The NaOH extract yielded a radiocarbon age of $10,540 \pm 130$ yr BP (SUA 28B).

Comparison of results from the two treatments suggests that humic acid contamination was probably not present (R. Gillespie, personal communication).

Approximately 7.5 km up the valley from the lowest till found, a lens of peat, buried beneath 4 m of till, was uncovered by pre-mining operations immediately north of the ore body at 3,620 m. The peat was sieved and large peaty wood pieces and the <50 mesh fraction dated separately. These gave dates of $11,330 \pm 150$ yr BP (SUA 29A) and $11,820 \pm 150$ yr BP (SUA 29B) respectively.

These findings indicate that a major advance of the Carstenz ice took place with a glacier reaching 3,500 m less than 11,300 yr ago and extending to 1,700 m less than 10,000 yr ago, with a length of about 15 km.

Ice in the Otomona Valley would have come from an accumulation area of 43 km². Up valley from the lowest glacial deposits, the Otomona is no more than 2 km wide, south facing and up to 2,000 m deep; it is thus well shaded. The active ablation area below 3,600 m to the lowest till deposit found would have been about 10–12 km². Given a suitable climate with high solid precipitation totals in a glacierized valley with such a contrast between the shape of the accumulation and the ablation areas we would expect that the terminal deposits would be at a very low altitude.

There is no indication in the literature that the time of advance of ice down the East Otomona Valley, reported above, was matched by ice advances in other tropical areas^{2,4,5}. On Mt Wilhelm⁶, P.N.G., deglaciation was complete at 3,550 m by $12,570 \pm 290$ yr BP (ANU 815, J. A. P., unpublished) and pollen analysis (G. S. H., unpublished) indicates no marked cold phase since then, although conditions at that time were colder than at present.

At present, ice accumulation in the Carstenz Mountains occurs down to 4,400 m. Precipitation probably exceeds 400 cm yr⁻¹ and comes predominantly from the south, particularly during the south-east tradewinds season³. Most of this moisture is derived from the warm Arafura Sea and Torres Strait which would have been dry land during the maximum of the glacial periods⁷. During that time winds from the south or south-east would have traversed the Australian continent and would have been relatively dry. The flooding of the Arafura shelf during the Flandrian transgression coincides with the time

of the East Otomona ice advance, and it seems possible that cloudiness and solid precipitation increased with the reflooding, resulting in the ice advance.

This interpretation suggests that the modern precipitation gradients across the Cordillera of New Guinea might not be a guide to the gradients that prevailed there during the full glacial periods. Hence it may prove impossible to correlate the major glacial events of ranges dominated by northerly sources of precipitation with those of areas mainly subject to the influence of air from southerly quarters and any correlations with areas further afield should also be subject to considerable caution.

The Carstenz Glaciers Expedition was supported by the ARGC and Freeport Indonesia. Dr U. Radok, Department of Meteorology, University of Melbourne, was chief investigator and C. Randell Champion was expedition leader. We thank Professor J. N. Jennings for assistance with the carbon dates and Mr A. Russel, mine manager, Ertsberg, and Forbes Wilson, J. Curry and Steele Ainsley of Freeport Indonesia for assistance to the field party.

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Fig. 1 Exposure of till at 1,705 m on the west bank of the channel of the East Otomona River, West Irian. Remains of trees are incorporated into glacial deposits (a) which have buried river gravels (b).

BIOLOGICAL SCIENCES

Delay of Parturition in the Rat by Anti-Inflammatory Agents which Inhibit the Biosynthesis of Prostaglandins

ASPIRIN and indomethacin inhibit the biosynthesis of prostaglandins in various tissues^{1–3} and similar effects have been seen with fenclozic acid⁴ and hydrocortisone⁵. This together with the growing evidence that prostaglandins, particularly PGF_{2α}, are involved in processes leading to the termination of luteal function and to parturition in several species^{6–8} prompted us to investigate the effects of some anti-inflammatory agents on the time of onset and course of parturition in the rat.

In preliminary tests these agents, given by mouth, were most effective in prolonging pregnancy, and least toxic, when administered on days 20 and 21 of pregnancy (day 1 being the day of a sperm-positive vaginal smear). Therefore, the compounds or vehicle (0.5% aqueous 'Tween 80') alone were given on these days at about 0930 h. Births of live and dead pups were recorded every two hours starting at 0800 h on day 22 and the time to the onset of parturition (TOP) was reckoned from this point.

Table 1 Effect of Anti-Inflammatory Compounds on the Time of Onset of Parturition (TOP) in the Rat

Compound	Dose mg/kg p.o.	No. of animals	Con- trols	Treated	Mean TOP (h) $\pm$ s.e.		Effect (h) $\pm$ s.e.	P compared with treated
					Con- trols	Treated		
Indomethacin	2	5	5		22.8	42.4	19.6	<0.02
					± 3.8	± 4.8	± 6.1	
	2	8	10		23.7	48.6	24.8	<0.01
Aspirin	200	9	8†		18.0	34.2	16.2	<0.01
					± 2.8	± 3.8	± 4.7	
	200	9	8†		18.0	34.2	16.2	<0.01
Fenclozic acid	25	10	10		18.4	48.0	29.6	<0.001
					± 2.4	± 2.9	± 3.8	
	50	5	10‡		22.4	56.4	34.0	<0.001
Cortisone acetate	50*	5	5		30.8	23.6	-7.2	NS
					± 8.6	± 2.5	± 8.9	
	50	5	5		18.0	18.0	0.0	NS
					± 3.7	± 2.9	± 4.7	

* Dosed subcutaneously.

† Two treated animals died before the normal time of parturition and are therefore not included in the calculations.

‡ One treated animal which had not littered by day 26 of pregnancy was assigned an arbitrary TOP of 90 h.

Fenclozic acid: (ICI 54,450) : [2-(4-chlorophenyl)-thiazol-4-ylacetic acid]¹². Effect=mean TOP of treated group minus mean TOP of controls.

All compounds tested except cortisone acetate delayed the onset of parturition (Table 1). The longest mean delay (34 h) was observed with fenclozic acid at 50 mg kg⁻¹ day⁻¹. Aspirin at 200 mg kg⁻¹ day⁻¹ or indomethacin at 2 mg kg⁻¹ day⁻¹ caused delays of 16–25 h. Of the effective compounds, fenclozic acid and indomethacin, but not aspirin, caused an increase in the proportion of pups born dead without, however, affecting significantly the mean number of all pups delivered per rat (Table 2).

Table 2 Effect of Anti-Inflammatory Compounds on the Number of Pups Born Dead and Number of Pups Delivered

Compound	Dose mg/kg p.o.	No. of animals	Con- trols	Treated	Pups born dead/total pups		Mean pups delivered per rat	
					Con- trols	Treated	Con- trols	Treated
Indomethacin	2	5	5		0/39	6/49	7.8	9.8
	2	8	10		7/74	36/78	9.2	7.4
Aspirin	200	9	8		6/95	4/70	10.5	8.7
Fenclozic acid	25	10	10		4/107	19/97	10.7	9.7
	50	5	9		0/55	74/98	11.0	10.9
Cortisone acetate	50*	5	5		1/45	3/55	9.0	11.0
	50	5	5		0/60	0/54	12.0	10.8

* Dosed subcutaneously.

These observations are consistent with the view that prostaglandins are essential for the timely onset and normal course of parturition in rats. This is supported by finding, in a subsequent experiment, that the administration of prostaglandin F_{2α} on day 20 prevented the delay in parturition and the stillbirths caused by the treatment with indomethacin (Table 3). Synthetic, racemic prostaglandin F_{2α}, 50 µg/rat in 0.1 ml. of phosphate buffer (pH 7.4) was given intraperitoneally at 0930, 1300 and 1430 h on day 20 of pregnancy, all other rats being dosed with buffer. Indomethacin was given as before (Table 2) and all other rats dosed in parallel with 'Tween 80'.

Premature parturition can also be induced in rats by intraperitoneal injection of prostaglandin F_{2α} a few days before the normal time of onset of labour. Deis⁹ reported that doses of the natural compound totalling 1.2 mg/rat on day 17 or 18 of pregnancy curtailed pregnancy by about 2 days. In similar experiments we found that 4/5 rats given racemic prostaglandin F_{2α} on day 19 of pregnancy in 3 intraperitoneal doses totalling 150 µg (2/3 rats) or 300 µg (2/2 rats) littered by day 21,

Table 3 Effect of Prostaglandin F_{2α} on Time of Onset of Parturition in Rats Treated with Indomethacin

Group	Treatment	No. of animals	Mean TOP (h) $\pm$ s.e.	Effect (h) $\pm$ s.e.	P compared with treated	Pups born dead/total pups	Mean pups delivered per rat
1	Controls	4	14.5	—	—	3/30	7.50
2	PGF _{2α} *	4	-3.0	-17.5	<0.1	3/42	10.50
			± 4.99	± 7.78			
3	Indomethacin	4	44.0	29.5	<0.02	14/33	8.25
4	Indomethacin + PGF _{2α} *	4	6.68	± 8.34	NS	2/24	6.0
			1.5	-13.0			
			± 6.8	± 7.9			

* Synthetic racemic prostaglandin F_{2α}.

whereas a majority (about 75%) of rats of our strain normally litter on day 23 of pregnancy and never before noon on day 22.

The precise role of prostaglandins in normal parturition is still unclear; the complexities of the situation are well illustrated by the recent work of Liggins *et al.* in the ewe¹⁰. In rats, where the ovaries seem to be the main source of progesterone throughout normal pregnancy, parturition is preceded by an abrupt fall in progesterone levels in the ovaries, uterus, placenta and peripheral blood and the hormone reaches low levels in the plasma by about day 20¹¹. Prostaglandin F_{2α} induces luteolysis at early stages of pregnancy in a number of species, including the rat. It is tempting to suppose that one function of prostaglandins in late pregnancy in rats is to induce pre-partum luteolysis; then the delay in the onset of parturition caused by the drugs mentioned in Table 1 might be explained by inhibition of the biosynthesis of the luteolytic agent resulting in delay in the fall in progesterone blood levels.

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Sex-Hormone-Binding Globulin is an Oestrogen Amplifier

We suggest a novel biological role for a specific plasma-binding protein in the regulation of oestrogen and androgen activity in man. The biological activity of oestradiol and

testosterone, as with other steroids¹, is probably exerted by the unbound fraction in plasma; this is only 1–3% of the total concentration. The plasma proteins that bind testosterone and oestradiol include sex-hormone-binding β globulin (SHBG)², which has high affinity for both steroids; and albumin, which has low affinity but is present in three thousand times the concentration. Further, corticosteroid-binding globulin (CBG) binds testosterone³ though its main affinity is for cortisol and progesterone.

The biological function of the specific steroid-binding globulins is unknown. It has been suggested⁴ that they protect steroids from degradation, and that they damp out rapid fluctuations in active unbound steroid concentration. We propose here that a further biological role of SHBG is regulation of the ratio of unbound testosterone to unbound oestradiol; and so it is a determinant of sex-hormone balance. Our hypothesis is as follows.

Testosterone and oestradiol bind to the same site on SHBG but testosterone is thought to bind more strongly than oestradiol². Changes in SHBG concentration may therefore alter the relative binding of the two steroids. Now, an increase in oestrogens raises SHBG concentration, while an increase in androgens reduces it^{5,6}; consequently an oestrogen-induced rise in SHBG might tip the balance between testosterone and oestradiol in favour of oestradiol, by preferentially binding testosterone. Conversely, an androgen-induced fall in SHBG might tip the balance in favour of testosterone by causing a greater proportional rise in unbound testosterone than in unbound oestradiol. We have carried out experiments *in vitro* to test this hypothesis.

Table 1 Apparent Equilibrium Constants (K_e) and Binding Site Concentrations (S), at 37° C

		Approximate K_e (M^{-1})		S (M)	
		SHBG	Albumin	SHBG*	Albumin
Testosterone†	Male	1.9×10^9	3.6×10^4	3.9×10^{-8}	5.0×10^{-4}
	Female	1.4×10^9	3.7×10^4	7.8×10^{-8}	5.5×10^{-4}
Oestradiol	Male	6.0×10^8	6.0×10^4	3.9×10^{-8}	5.0×10^{-4}
	Female	6.4×10^8	5.1×10^4	7.8×10^{-8}	5.5×10^{-4}

* Determined from Rosenthal plots using 3H -dihydrotestosterone to avoid interference from CBG binding.

† Carried out in the presence of 2.7 μM cortisol to minimize interference from CBG binding.

We used steady-state gel filtration⁷ to measure the percentage binding of 3H -testosterone or oestradiol (6×10^{-10} M and 1×10^{-10} M respectively) at 37° C and pH 7.4 in undiluted serum samples which had been freed of endogenous steroids⁸. The apparent equilibrium constant, K_e , and binding site concentration, S , were determined by Rosenthal's method⁹.

The observed binding constants are shown in Table 1, and are consistent with previous estimates^{2,6,10–12}. The most striking feature is that at 37° C testosterone binds more than twice as strongly to SHBG as does oestradiol, but with albumen oestradiol binds twice as strongly as does testosterone. This suggested that the relative binding of testosterone and oestradiol might depend on the relative concentrations of SHBG and albumin, and that a rise in SHBG concentration would cause a greater increase in the binding of testosterone than that of oestradiol.

We have shown that this effect actually occurs by varying the SHBG concentrations in serum independently of albumin, and measuring unbound testosterone and oestradiol at the various SHBG concentrations. We mixed pregnancy serum, normal female serum, male serum and male serum in which SHBG had been destroyed at 60° C, in various proportions; the albumin concentrations were approximately constant. The results (Fig. 1) show that as SHBG concentration rises over the physiological range, unbound testosterone falls more

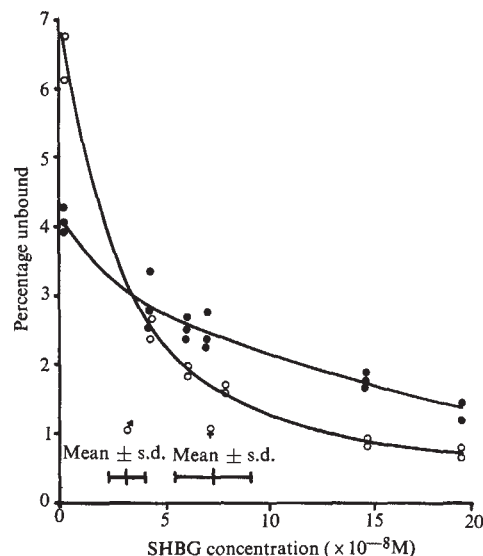


Fig. 1 Percentage unbound testosterone (○—○) and oestradiol (●—●) at 37° C, related to serum concentration of SHBG. Testosterone concentration 3.6×10^{-9} M, oestradiol concentration 2×10^{-10} M. The horizontal bars indicate the mean $\pm$ s.d. concentration of SHBG in normal males and females aged 20–40, found in our laboratory. These were estimated from Rosenthal plots and by reversed saturation analysis¹³, using dihydrotestosterone as ligand.

rapidly than does unbound oestradiol. Conversely, as SHBG concentration falls, the ratio of unbound testosterone to unbound oestradiol rises. The data clearly support the hypothesis that SHBG concentration is a major determinant of the ratio of unbound testosterone and oestradiol, at given total concentrations of the two.

Table 2 Steroid Competition for Serum Binding Proteins at Physiological Steroid Concentrations

	Tracer only	Testosterone added 3.5×10^{-8} M	Oestradiol added 3.6×10^{-8} M
3H -oestradiol unbound (%)			
Male serum	2.84	2.68	2.62
Female	2.54	2.36	2.34
Late pregnancy	1.35	1.53	1.53
3H -testosterone unbound (%)			
Male serum	2.41	2.72	3.38
Female	1.68	1.63	2.11
Late pregnancy	0.81	0.92	—

Overall equilibrium changes shown by percentage unbound of tracer testosterone or oestradiol, with and without added amounts of the unlabelled steroids. Tracer (3H) testosterone = 3.6×10^{-9} M, tracer (3H) oestradiol = 2×10^{-10} M.

This relationship between unbound testosterone and oestradiol might be altered by steroid competition for the same binding site on SHBG—notably displacement of the very small amounts of oestradiol in serum by the larger amounts of testosterone with its higher binding affinity. We tested this by measuring the binding of 3H -oestradiol in the presence of added testosterone, and vice versa. The results (Table 2) show that oestradiol was not significantly displaced into the unbound state by testosterone added at physiological concentrations (those not greater than the binding capacity of SHBG). Calculation showed that the competition for SHBG binding sites resulted mainly in displacement of bound 3H -oestradiol from SHBG to albumin. Similarly, added oestradiol displaced only a little bound 3H -testosterone into the unbound state over the physiological range of concentrations, the added oestradiol being relatively more bound to albumin than to SHBG. (We concede that displacement into the unbound state would be more apparent at higher steroid concentrations.)

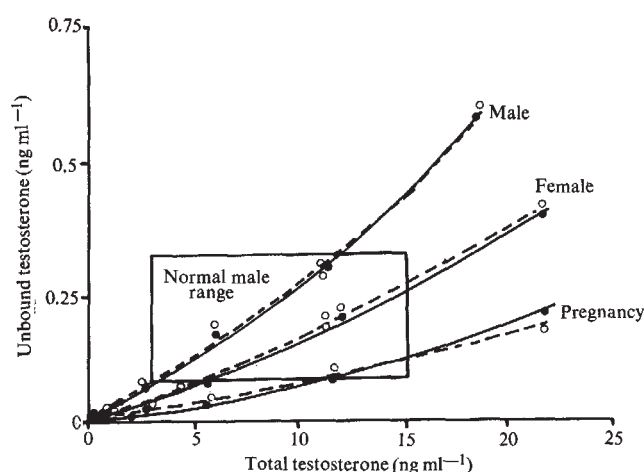


Fig. 2 Absolute unbound testosterone concentration and total testosterone concentration at 37° C, with and without added cortisol. A pair of lines is shown for each male, female and late pregnancy serum, and the box indicates the physiological male range for testosterone concentrations. ●—●, Without added cortisol; ○---○, with cortisol (2.8 μ M). Cortisol (4.7 μ M) in diluted serum (1:3) caused considerably more displacement, which would be expected as testosterone binding would be weakened by dilution.

We were also concerned that physiological fluctuations of cortisol might significantly change unbound testosterone concentration, by displacing testosterone bound to CBG—as suggested by Lea and Støa¹⁴ from experiments at low temperature. In fact very large concentrations of cortisol (2.8 μ M) caused little increase of unbound testosterone at 37° C over a wide range of SHBG and testosterone concentrations, as shown in Fig. 2. Calculation from our data indicated that the addition of the cortisol led mainly to a rearrangement of the bound testosterone between the various binding proteins, rather than to an increase in unbound testosterone.

Thus our findings support the idea that SHBG is an important determinant of the ratio of unbound testosterone and oestradiol. If the sex-hormone balance of an individual is determined by this ratio then changes of SHBG concentration may have

important biological consequences. Increased SHBG concentrations will have a feminizing influence and decreased concentrations a masculinizing influence. Where such changes are induced by oestrogens or androgens themselves, a self-servo action is to be expected. For example, oestrogens will promote their own action by increasing SHBG and so the ratio of unbound oestradiol to testosterone (Fig. 3); conversely, androgens will promote their own action by reducing SHBG and increasing the ratio of unbound testosterone to oestradiol. We therefore propose that SHBG may have an important role as a biological amplifier for sex-steroid action.

Our hypothesis gains support from the finding of altered SHBG concentrations in a number of endocrine disorders. For example, SHBG levels are generally lower in women with hirsutes and the polycystic ovary syndrome^{6,15-17}. In pregnancy, the high SHBG levels may prevent virilization of the mother or foetus by high androgen levels. Other factors may alter SHBG concentration with endocrine consequences. For example, in thyrotoxicosis and after triiodothyronine administration SHBG concentration increases considerably¹⁸, with resulting changes in oestradiol and testosterone metabolism consistent with our hypothesis. In the male there are increased circulating gonadotrophin levels, and the total testosterone level increases as a result of gonadal stimulation, until the free concentration returns to normal. The oestradiol production also rises in proportion¹⁹, but because of its weaker binding to SHBG the unbound concentration must rise more than unbound testosterone. This could account for the frequently seen gynecomastia in thyrotoxicosis. We suggest that this role of SHBG in the maintenance or alteration of sex differentiation in the adult requires exploration.

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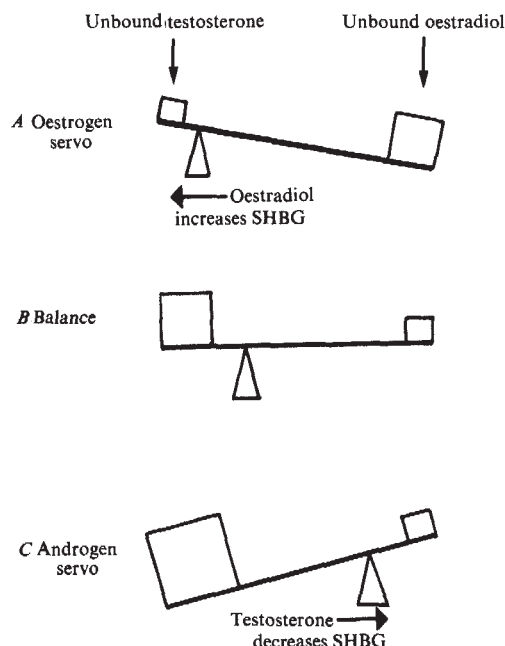


Fig. 3 Testosterone-oestradiol balance and SHBG concentration. SHBG is denoted by the fulcrum, which moves in response to oestradiol or testosterone; the movement of the fulcrum increases the tendency of the balance to tip in the direction of unbound oestradiol or testosterone, as the case may be.

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Immunological Cross-reactivity of Antigens common to Tumour and Foetal Cells

THERE has been a resurgence of interest and activity related to tumour-associated foetal substances¹⁻³. It is not yet clear whether the various foetal or carcinoembryonic systems represent *de novo* synthesis characteristic of foetal or neoplastic states or whether they simply represent unmasked structural complexes of the cell membrane. We presented evidence suggesting that spleen cells infected with RNA tumour virus, as well as a transplantable plasma-cell tumour (PCT), possessed foetal antigen^{4,5}. The protection afforded by foetal-antigen immunization in these systems agrees with recent findings for tumours induced by DNA viruses in hamsters⁶⁻⁹. The effect of foetal-antigen immunization on the growth of PCT was considered important since it has been demonstrated¹⁰ that this particular transplantable tumour possessed a high level of foetal-type tRNA suggesting that the altered gene groups in the PCT line direct production in the tumour cells of embryonic or foetal antigens that cross-react with foetal-antigen-induced antibody.

Preliminary attempts to prevent the development of subcutaneous embryomas, induced with whole foetal homogenates, in intact hamsters immunized with SV40 tumours have been unsuccessful although in this system foetal-cell immunization has a suppressive influence on tumour growth⁷. Quantitative assay of immunological cross-reactivity between antigens on foetal and tumour cells is particularly important as it was demonstrated recently that the common antigen of foetal and tumour cells is distinct from the tumour-specific transplantation antigen, at least in chemically induced rat tumours¹¹. We present a quantitative *in vivo* assay to test for cross-reactivity between foetal-cell and tumour-cell antigens by using a modified colony-forming unit (CFU) technique¹². We selected foetal liver as an immunogenic and test-cell population because: (1) this population of cells is primarily haematopoietic¹³ and upon adoptive transfer to irradiated recipients proliferates to form clonal colonies in the spleen^{12,14}; (2) histological and ultrastructural examination of the whole-foetal preparation used for immunization showed that the major intact cells were morphologically identical to erythroblasts^{4,5}; (3) studies have shown that in rat and mouse systems, immunization with foetal liver cells suppresses growth of implanted tumours to a greater degree than did immunization with foetal-minus-liver cell preparations¹⁵. We concluded that expression of characteristic foetal or carcinoembryonic antigens is probably greater in haematopoietic precursors than in the whole foetus.

First litters from 8-week-old BALB/c (specific-pathogen-free) mice were used as a source of foetal tissue. Timed matings were achieved during the night and the number of vaginal plugs was recorded the following morning; the plug date was considered day zero. A BALB/c plasma-cell ascites tumour (passage number 31), originally induced by mineral oil, was propagated by intraperitoneal injection of 1×10^6 ascites cells into syngeneic adult male mice. Uteri were taken from primiparous mice on selected days; methods of preparing cell suspension of whole foetus or foetal liver have been

described^{4,5}. Cell concentrations and dilutions of the inoculant were based on the number of eosin-excluding cells. All suspensions of foetal cells, PCT suspensions, and homologous or heterologous erythrocytes used for immunization were exposed to 5,000 r. of X-rays at a dose rate of 500 r./min.

Eight to ten-week-old BALB/c male mice were immunized intraperitoneally with either 10^7 viable (eosin-excluding), 5,000 r.-irradiated foetal cells, given five times over a 2-week period, or 10^7 irradiated plasmacytoma cells, given once a week for 3 weeks. They were irradiated (750 r.) 7 days after the last immunizing dose providing a parenchymal cell depleted, splenic environment for colony formation.

A comparison was made of foetal colony forming units (FCFU) resulting from injection of various doses of 15-day-old foetal liver cells into irradiated adult male recipients previously immunized with foetal liver cells, foetus-minus-liver cells, or whole embryo cells. We used the colony-forming assay as described by Till and McCulloch¹². Fifteen-day-old foetal liver cells were diluted in Hanks solution containing 1% of isologous mouse serum. Immunized and normal mice were X-irradiated (750 r.) and, 24 h later, injected intravenously with 5×10^5 foetal liver cells in a constant volume of Hanks. Eight days after injection, animals were weighed, spleens were removed, and placed in Bouin's fixative. The following day, surface colonies of spleens were counted under a dissecting microscope ($\times 10$). We selected 15-day-old foetal liver for the foetal colony-forming unit (FCFU) assay because preliminary experiments showed that a more consistent number of erythroid colonies was produced at that period of gestation. Table 1 shows that suppression of FCFU occurs for all cell doses in recipients immunized with foetal liver cells. Suppression was approximately 35% with the 0.25, 0.75, and 1.0×10^6 foetal liver cells and 55% with 0.5×10^6 cells. Recipients immunized with foetus-minus-liver or whole-foetus cells showed no suppressive effect except at high foetal-liver-cell doses. It appears that not all foetal tissues express the same antigenicity at a specific gestation period. Strongest suppression is achieved with foetal liver cells at a dose of 0.5×10^6 , and this dose was selected for assessing FCFU in immunized recipients.

We measured the effect of PCT immunization on FCFU in recipients in which adoptive transfer of foetal liver cells from 13-, 14-, and 15-day-old fetuses was made. Greatest suppression was achieved with 15-day-old cells (Table 2A). FCFU were also examined at 1, 2, and 3 weeks after immunization with PCT. The degree of suppression is less at the second and third week after the last PCT injection (Table 2B), suggesting that the levels of efficacy of the humoral factor diminish with time.

We were concerned about the possible complication of immunization with nonspecific antigens and how it might modify the seeding and growth of FCFU in recipient spleens. We compared the effect of immunization with PCT, homologous C57BL/6 erythrocytes, and heterologous sheep erythrocytes. The response of animals immunized with C57BL/6 or sheep erythrocytes did not differ significantly from untreated controls (Table 3), although increased spleen weights were detected in these immunized recipients prior to and after irradiation. Significant suppression was seen when animals were immunized with PCT.

Table 1 Effect of Foetal-Cell Immunization on FCFU

Recipients' pretreatment	Spleen-colony count with foetal liver cell dose (millions)*			
	0.25	0.50	0.75	1.0
Immunized 5 times with foetal liver cells	4.6 $\pm$ 0.5†	6.5 $\pm$ 0.4†	14.3 $\pm$ 0.5†	16.2 $\pm$ 0.4†
Immunized 5 times with foetus-minus-liver cells	8.0 $\pm$ 0.6	14.0 $\pm$ 0.6	16.3 $\pm$ 0.9†	19.8 $\pm$ 0.9
Immunized 5 times with whole foetus cells	8.0 $\pm$ 0.3	12.1 $\pm$ 0.5	13.8 $\pm$ 0.6†	17.4 $\pm$ 1.1†
Untreated controls	6.9 $\pm$ 0.5	14.2 $\pm$ 0.6	21.3 $\pm$ 0.4	22.8 $\pm$ 0.5

* Each point represented the mean $\pm$ s.e. of 10 mice.

† Significant difference from control at the level of $P \leq 0.01$ as calculated by Dunnett's test for multiple comparison with control.

It was important to determine whether humoral factors generated as a result of PCT would also show a suppressive effect on the CFU potential of adult bone marrow stem cells. No significant depression of bone marrow CFU, measured 8 days after injection, in the spleens of irradiated recipients in any of the experimental groups was demonstrated.

Our results clearly show that a suppressive effect does not occur in PCT-immunized animals with another rapidly proliferating cell population, but does occur when tested against foetal liver cells. We wished to elucidate specific aspects of antigen cross-reactivity between these two cell populations. Groups of animals were immunized three times with PCT. Simultaneously with the last immunization, some of the animals were injected subcutaneously with foetal liver cells, either irradiated or nonirradiated. A significant difference in FCFU is again found in the animals immunized with PCT compared to nonimmunized controls (Table 4). A similar suppression of FCFU was found in PCT-immunized animals receiving a booster of irradiated foetal liver cells subcutaneously. Little suppression of FCFU was noted, however, in animals immunized with PCT and given a viable foetal-liver-cell booster.

This suggests that the embryoma, growing subcutaneously as a result of injections of live foetal liver cells in adult animals immunized previously with PCT, absorbs antibody during the weekly interval between the last immunization and the irradiation and adoptive transfer into the immunized recipients. Absorption of antibody does not occur when the nonviable

irradiated foetal-liver booster is injected subcutaneously, when the antibody can exert its suppressive effect on FCFU.

Our results, obtained by use of an *in vivo* transfer system, strongly suggest an immunological cross-reactivity between common antigen(s) of BALB/c plasmacytomas and foetal cells, with the strongest reactivity detected in foetal liver cells. The basis of this immunological phenomenon is presumed to be a humoral antibody because: (1) histological examination, prior to irradiation, of spleens of recipients immunized with plasmacytoma of foetal liver showed hyperplastic germinal centres and a morphology of lymphatic nodules generally associated with humoral antibody production; (2) absorption or neutralization of this factor was achieved by subcutaneous injection of foetal cells; (3) the humoral factor existed and exerted its influence after irradiation of hyperimmunized animals, and this influence was expressed for at least 3 weeks after the last treatment of the recipients. We have not directly tested cell-mediated immunity in this system, and so we do not eliminate the involvement of this component of host-immune reaction^{16,17}.

On this basis and given the high statistical resolution of this modified CFU assay, we strongly suggest that this assay can be used as an accurate *in vivo* test to detect immunological cross-reactivity between common antigens of a variety of tumour and foetal-cell inocula, even in xenogeneic systems, because syngeneic foetal liver cells are always the test-cell dose.

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Table 2 Effect of Plasmacytoma-Cell Immunization on FCFU

Recipients' pretreatment	Spleen-colony count with foetal liver cells (5×10^5)*		
	13 days	14 days	15 days
A. Immunized 3 times with plasma-cell tumour	$7.4 \pm 0.7^\dagger$ (10)	$8.0 \pm 0.6^\dagger$ (20)	$4.2 \pm 0.5^\dagger$ (20)
Untreated controls	12.6 ± 0.9 (27)	12.6 ± 0.6 (10)	11.3 ± 0.6 (32)
B. Immunized 3 times with plasma-cell tumour	1st week	2nd week	3rd week
	$4.2 \pm 0.5^\dagger$ (20)	$7.8 \pm 0.5^\dagger$ (20)	$6.4 \pm 0.3^\dagger$ (23)
	Untreated controls	11.3 ± 0.6 (32)	15.6 ± 1.0 (10)

* Each point represents the mean $\pm$ s.e. The number of mice per point is in parentheses.

† Significant difference from control at the $P \leq 0.001$ level.

Table 3 Comparison of Specific and Nonspecific Immunization on Adult Bone Marrow (CFU) and Foetal Liver (FCFU)

Recipients' pretreatment	Foetal liver cells (5×10^5)	Spleen-colony count*	
		Adult bone marrow cells (2×10^5)	Without foetal liver cells
Immunized 3 times with plasma-cell tumour	$6.8 \pm 0.5^\dagger$ (14)	25.7 ± 0.9 (10)	0.1 ± 0.1 (15)
Immunized 3 times with C57BL/6 erythrocytes	11.0 ± 0.3 (20)	27.9 ± 0.3 (15)	0 (10)
Immunized 3 times with sheep erythrocytes	12.9 ± 0.8 (14)	27.1 ± 0.7 (15)	0.1 ± 0.1 (10)
Untreated controls	11.9 ± 0.6 (15)	27.7 ± 0.5 (15)	0 (10)

* Each point represents the mean $\pm$ s.e. The number of mice per point is in parentheses.

† Significant difference from control at the $P \leq 0.001$ level.

Table 4 Immunological Cross-reactivity Between PCT and Foetal-Liver-Cell Antigen(s)

Recipients' post-treatment	Subcutaneous booster	Spleen-colony count with foetal liver cells (5×10^5)*	
Immunized 3 times with plasma-cell tumour	None	$6.8 \pm 0.5^\dagger$ (14)	
Immunized 3 times with plasma-cell tumour	Foetal liver cells (live)	13.1 ± 0.4 (14)	
Immunized 3 times with plasma-cell tumour	Foetal liver cells (X-rayed)	$7.9 \pm 0.5^\dagger$ (14)	
Untreated controls	None	15.3 ± 0.4 (15)	
		Spleen-colony count without foetal liver cells	
Immunized 3 times with plasma-cell tumour	None	0.1 ± 0.1	(10)

* Each point represents the mean $\pm$ s.e. The number of mice per point is in parentheses.

† Significant difference from control at the $P \leq 0.001$ level.

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Growth of *Chlamydomonas* in a Medium containing Mercury

WE have studied the behaviour of the alga *Chlamydomonas* grown in a medium containing mercury with a view to the removal of mercury from sewage and industrial wastes by algal treatment processes. It is already known that in several algae, and other aquatic organisms, there is an accumulation of mercury in the cells whenever mercury is present in the growth media¹, and that when mercury is present in the growth medium, there is a lag period in the development of a *Chlorella* culture².

We describe here the behaviour and special features of a *Chlamydomonas* culture grown on medium containing mercury.

A pure culture of *Chlamydomonas reinhardtii* y^{-1} was grown on a sterile medium³ containing acetate, citrate and minerals; penicillin was added to concentration of 100 U ml.⁻¹. Mercury at various concentrations was provided as HgCl₂ or ²⁰³HgCl₂. The algae were sown as a starting culture of 80–100 cells/ml. $\times 10^{-3}$, and a mixture of CO₂ (5%) in air was bubbled through at a rate of 30 ml./min. The final volume of the culture was 2 l. grown with continuous stirring in a 3-l. Erlenmeyer flask. No bacterial contamination was detected in the culture during

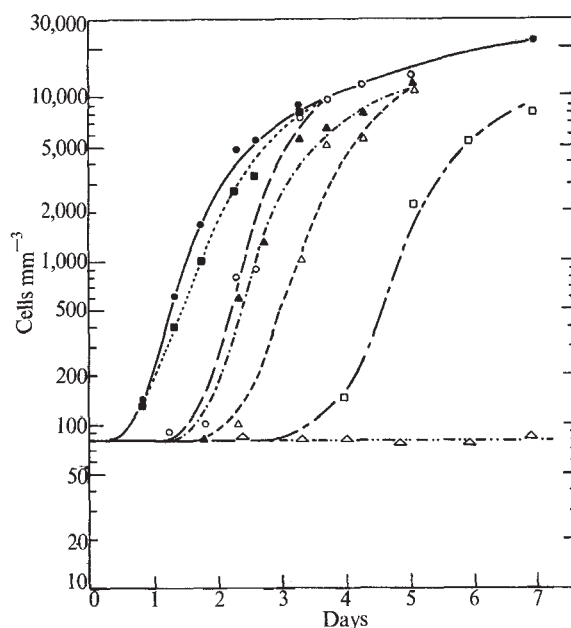


Fig. 1 Growth of *Chlamydomonas reinhardtii* in media containing various inorganic mercury (HgCl₂) concentrations (mg/l.). ●—●, Control; ■—■, 0.1; ○—○, 0.17; ▲—▲, 0.2; △—△, 0.25; □—□, 1.0; △—△, 2.0.

growth. The cultures were continually illuminated with 1,000 foot-candles of fluorescent light.

Raising the initial mercury concentration gradually from 0 to 1.0 mg/l. caused an increasing lag period in the growth (Fig. 1). In the culture grown on a medium containing 2 mg/l. mercury, growth was completely retarded.

We then used ²⁰³HgCl₂ in the medium; total mercury was determined from corrected activity measurements. The mercury concentration used was 0.2 mg/l. and as a control we used a growth medium containing a ²⁰³HgCl₂ concentration of 0.16 mg Hg/l. with no algae. The culture was vigorously stirred before sampling to include any sediment in samples withdrawn. Figs. 2 and 3 show that ²⁰³Hg cultures behave similarly to non-radioactive Hg cultures (Fig. 1). The mercury concentration in the whole culture (medium+cells) decreased by 40% in the 8 days of the experiment (Fig. 2a); in the control there was a 5% decrease (Fig. 2b). The change in mercury concentration

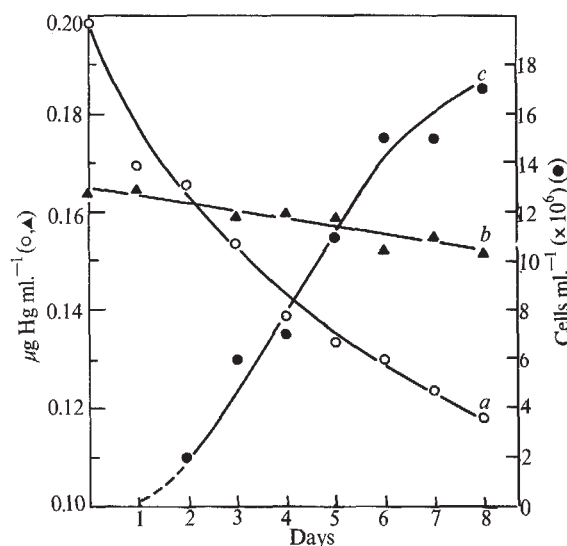


Fig. 2 Decrease in mercury concentration during the growth of *Chlamydomonas reinhardtii*. Mercury was provided as ²⁰³HgCl₂. a, Mercury concentration in the whole culture (medium+cells). b, Mercury concentration in unseeded control medium. c, Growth of the culture.

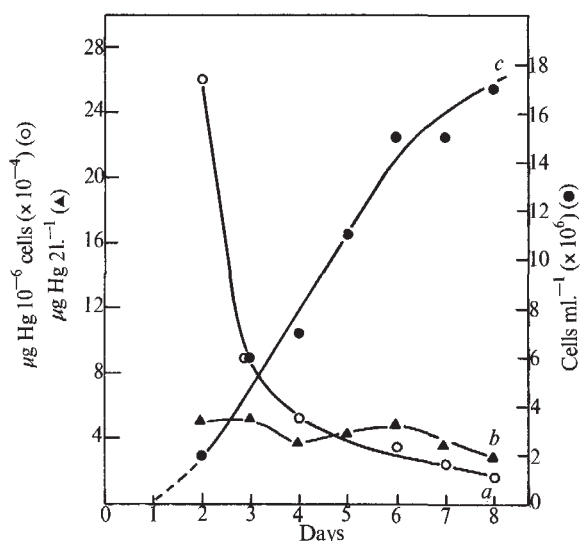


Fig. 3 Variance in mercury content in the biomass during the growth of *Chlamydomonas reinhardtii*. Mercury was provided as $^{203}\text{HgCl}_2$. a, Mercury content in the biomass (per 10^6 cells). b, Mercury content in biomass removed from a unit volume of culture. c, Growth of the culture.

was essentially in the medium alone, as only 2–2.5% of the total culture radioactivity appeared in the cells. It seems that the reduction of mercury content is a result of its loss from the system. Most of the removal of mercury was due to the algal cells, and became slower in the course of the experiment. During the experiment, the radioactivity in the cells was measured in equal volumes of culture after centrifuging and washing twice in a solution of non-radioactive HgCl_2 (5 mg Hg/l.). The amount of mercury in or bound to the cells, which had been removed from equal volumes of media, did not change significantly with time though the culture continued to multiply (Fig. 3b), and the relation between the fresh weight of the biomass and the concentration of cells varied only over a range of 10%, indicating that changes in cell size were not an important factor. The amount of mercury per cell decreased by 90% from the 2nd to the 8th day (Fig. 3a). In the same period the total mercury of the culture decreased by 30% (Fig. 2a).

One of the important points to emerge is the ability of the cells to recover from the growth lag induced by mercury. During the lag (1.5 days) the mercury concentration in the medium fell from an initial 0.2 mg/l. to 0.17 mg/l. (Fig. 2a). This lower concentration of mercury (0.17 mg/l.), however, caused a similar lag if algal cells were introduced initially into it (Fig. 1). It seems, therefore, that overcoming this lag is not due to the lowering of the mercury concentration alone. Most of the loss of mercury is a direct outcome of the presence of algae in the medium and the process was particularly active during the lag period when the culture included essentially only the cells of the original inoculum.

This phenomenon may be due to a change in the mercury to a form which is volatile and less permeable, or which has less affinity to the cells. This change occurs through metabolic processes. Biotransformation of mercury in association with microorganisms has been observed in at least three other species; the bacterium *Pseudomonas* K-62 strain transformed some organo-mercury compounds to the free metal⁴; inorganic or phenylmercury was methylated by bacteria in natural sediments⁵; and *Neurospora crassa* is able to methylate inorganic mercury through a different metabolic pathway⁶.

Kamp-Nielsen in his work with *Chlorella*² suggested that the binding of Hg to insensitive sites in the cells might be responsible for ending the initial inhibition of growth. We do not agree with this interpretation of our findings in which decrease in the medium mercury concentration with time was accompanied by a three-fold decrease in cell-bound mercury. Nor is it a case

of mutant selection. Assuming the common microbial probability of 10^{-6} for a mutation to occur, and 10 h to be the generation time by which every cell gives four daughter cells, we could expect development of a mercury-resistant culture of similar growth rates from an initial concentration of 100,000 cells/ml. only 4 days after inoculation. In our experiment the lag was less than 2 days.

We suggest that the mercury changed into volatile form through some biological process, thus allowing it to leave the system. At the same time the permeability or the affinity to the cells was reduced. The mechanism of mercury loss may have application to the removal of mercury contamination from waste water.

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Bacterial Reduction of Arsenate in Sea Water

ARSENIC in the ocean exists primarily as arsenite and arsenate and thermodynamic calculations¹ indicate that in oxygenated sea water at pH 8.1, the equilibrium ratio of the activity of arsenate to arsenite should be about 10^{26} . But observations^{2–4} suggest that the ratio is, in fact, in the range 10^{-1} to 10^1 , far from the equilibrium value. My experiments with the inorganic oxidation of added sodium arsenite in surface Sargasso Sea water (in preparation) suggest that, at natural concentrations, all arsenite should be oxidized to arsenate in a matter of weeks or months. The fact that significant quantities of arsenite have been found in all oceanic regions examined is therefore puzzling unless some steady state mechanism can be discovered to account for it.

Because of a possible analogy to the bacterial reduction of iodate⁴, which is the probable mechanism maintaining the IO_3^-/I^- ratio at a value distinctly different from its thermodynamic equilibrium value¹, I have studied the bacterial reduction of arsenate in sea water. The several reports^{5–7} on the capacity of bacteria to reduce arsenate^{7–9} do not include marine bacteria.

Bacteria were grown in Guillard's⁸ medium "f" (omitting silicate) diluted 1 to 50 with Sargasso Sea water and enriched with 4.1% sucrose. Sargasso Sea water was collected from a depth of 2–4 m, and was stored, without filtration, in polyethylene lined drums for 6–9 months before use. Bacterial cultures from Narragansett Bay (NB culture) were obtained from phytoplankton filtered from the Bay water with a 20 μm net. A 2 g portion of the wet plankton mass was scraped off, mixed with about 100 ml. sterile Sargasso Sea water, and allowed to stand for a few days. Sterile media samples were then inoculated from the resulting supernatant liquid.

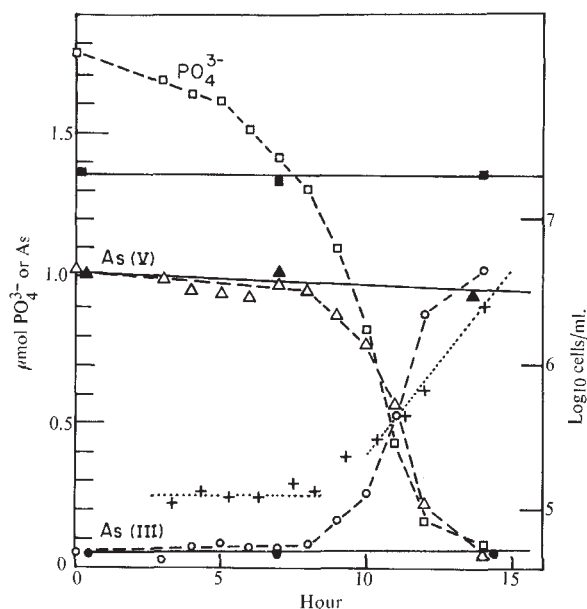


Fig. 1 Phosphate, arsenate, and arsenite concentrations and bacterial cell numbers as a function of time. $\square$, $\blacksquare$, Phosphate; $\triangle$, $\blacktriangle$, arsenate; $\circ$, $\bullet$, arsenite; +, cell numbers. Controls represented by solid symbols.

Cultures from the Sargasso Sea water (SS culture) were obtained simply by the dilution of the sterile "f" medium with non-sterile Sargasso Sea water.

The bacteria were not from a pure culture, but most of the organisms were motile rods. The NB culture was largely non-colonial, and the SS culture was colonial. A small number of coccoid bacterial forms were present in both cultures.

Arsenate reduction experiments were conducted in aerated medium at 20–22°C. Sodium arsenite was added to the sterile medium, and bacterial inoculum in log phase of growth was added. Concentrations of arsenite [As(III)], arsenate [As(V)], and soluble reactive phosphate were periodically determined using the spectrophotometric method of Johnson and Pilson⁹.

Results of an experiment with the non-colonial NB culture are given in Fig. 1. The concentrations of phosphate, arsenate, and arsenite in filtered aliquots (0.45 μ membrane of the culture medium) are plotted against time. Bacterial cell numbers were obtained by direct counts of cells using a haemocytometer and a phase microscope. No attempt was made to distinguish viable from non-viable cells. As the initial inoculum was made from a log phase culture, however, and the experiment was of short duration, it seems likely that most of the cells were alive when counted. Phosphorus and arsenic species in the control flask remained nearly constant.

During the experiment phosphate steadily decreased, suggesting accumulation in the bacteria or conversion to an unreactive phosphate species. Lear's work¹⁰ suggests the former to be more likely. As the bacterial population entered log phase growth (at about 8 h), arsenate began to be replaced by arsenite. The total arsenic remained constant and there was no evidence of accumulation by the bacteria. The arsenate reduction rate, calculated at 12 h, was about 10^{-11} μ mol cell⁻¹ min⁻¹. The oxygen concentration of the medium, measured three times during the experiment, was nearly constant, and averaged 4.76 ml. l⁻¹.

That bacterial arsenate reduction can be demonstrated in sea water under laboratory conditions suggests that such processes can occur in the open ocean, and may partly explain the observed arsenite concentrations. This is particularly true of surface waters, where bacterial productivity is high^{11,12}, and where factors of temperature, pressure, and nutrition are not as restrictive as in the abyssal zones. This reduction may also explain the occurrence of arsenite in the deep ocean, but

further studies in the problem must await advanced microbiological techniques for studying bacterial populations.

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Identification of Substrates and Isolation of Microorganisms responsible for Ethylene Production in the Soil

MICROORGANISMS seem to be responsible for the occurrence of ethylene in anaerobic soils at concentrations which can affect the root extension of cereals^{1–4}, for little ethylene is formed in sterilized soil. Evolution of the gas is unaffected by drying the soil at 35°C for two days and subsequently wetting under anaerobic conditions, so spore-forming organisms are probably responsible. The storage of soil at field capacity for an extended period inhibited the production of ethylene but this did not occur if plants had been grown in the soil or if the soil had been dried and heated to moderate temperatures, suggesting that substrates produced by plants or released during drying are important for the production of ethylene. Here we report an examination of the organisms responsible and the nature of the substrates.

A heavy clay (Evesham Series, Lower Lias) containing 5.3% organic matter was used. Soil particles were incubated on undefined microbiological media and on defined mineral

Table 1 Incubation of Soil Particles on Various Nutrient Media

Medium	Ethylene produced (p.p.m.)
(a) Basal mineral salts media with added carbon at 1% w/v	
Glucose + DL-methionine	2.5
DL-Methionine	0.2
L-Methionine	0.1
Acetate	0.1
Glucose	<0.1
Pyruvate	<0.1
(b) Undefined media	
Sabouraud dextrose agar + streptomycin	0.1
Tryptone soya agar	0.1
Nutrient agar	<0.1

Soil particles (less than 1 mm diameter) were added to the agar culture media (10 ml.) in screw-capped bottles (30 ml.) and incubated at 25°C. Ethylene was assayed by gas chromatography after 7 days. Uninoculated controls on each of the agar media produced less than 0.1 p.p.m. ethylene.

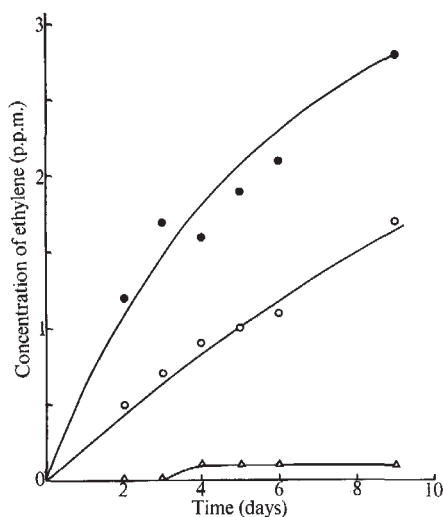


Fig. 1 Effect of substrates on the production of ethylene by the soil. Soil (100 g) was added to a flask (capacity 325 ml.). Each substrate (0.5 g) was added as a solution in water. The total volume of water added to each flask was 50 ml. The suspension and gas phase were saturated with nitrogen. ●, Glucose + methionine; ○, glucose; △, no substrate.

salts media containing precursors of ethylene in higher plants^{5,6}. Most ethylene was produced on mineral salts-glucose-methionine agar medium, on which the dominant constituent of the microbial population was shown to be *Mucor hiemalis* (Table 1). In pure culture, *M. hiemalis* and two unidentified soil yeasts produced large quantities of ethylene when grown on the mineral salts-glucose-methionine agar, but none when grown on malt or Sabouraud dextrose agar (Table 2).

Ilag and Curtis⁷ have shown that ethylene is commonly produced by fungi, and of the fungi they studied *Aspergillus clavatus* produced most. This fungus was examined under the same conditions as the soil isolates. It required glucose and methionine for ethylene synthesis, but produced less than 10% of the amount produced by *M. hiemalis*. To determine whether ethylene synthesis is common in the genus *Mucor*, another common soil species, *M. racemosus*, was examined. On the glucose-methionine medium it produced less than 3% of the amount of ethylene produced by *M. hiemalis*.

Our results suggest that *M. hiemalis*, which is common, and possibly the two yeasts may be an important source of ethylene in the soil. *M. hiemalis* shows a pronounced predilection for organic particles⁸ and dead plant tissue⁹, which presumably contain the necessary substrates for ethylene synthesis.

There is evidence that in the soil, as in pure microbial cultures, glucose and methionine are important substrates for the production of ethylene. Field sampling of the soil atmos-

phere showed that negligible ethylene was produced during the winter, when the soil had had a high water content for some months. Soil samples collected in winter produced no ethylene under anaerobic laboratory conditions whereas samples collected during the previous summer evolved appreciable quantities. The ability of the soil to produce ethylene was, however, restored when methionine and glucose were added (Fig. 1). The addition of these substrates had little effect when ethylene was already being evolved in appreciable quantities.

The requirements of glucose and methionine as substrates for the production of ethylene may explain why some pathogens have been shown to produce ethylene on living plant tissue but little or none on general microbiological media¹⁰⁻¹².

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Prehistoric Man at Lake Mungo, Australia, by 32,000 years BP

ALTHOUGH abundant evidence exists for human occupation of Africa and Eurasia for tens of thousands of years, man has often been considered a late-comer to the Australian continent. Archaeological investigations in Australia are now providing evidence of man between twenty and thirty thousand years ago, and one source is the long transverse dunes (lunettes) surrounding many ancient lakes of inland south-eastern Australia. During the Late Pleistocene the fresh waters of the lakes attracted early man and the lunettes built up on their north-eastern shores provided a favourable environment for preserving traces of occupation. Lake Mungo, one of a chain of lakes in south-western New South Wales, is now dry and its lunette is eroding and yielding ancient Aboriginal relics (Fig. 2).

The discovery of stone artefacts and ancient human remains in the lunette¹ prompted a detailed archaeological study of the area (H. A.) and led to archaeomagnetic measurements on some Aboriginal fireplaces (M. B.). We here review radiocarbon ages from Lake Mungo and establish that the area was occupied by 32,000 BP.

Fig. 1 shows five sites around the shores of Lake Mungo which contain evidence of man before 24,000 BP. The first four are within the Mungo soil-sedimentary unit¹ of the lunette, while site 5 lies between Lake Mungo and Lake Leagur. Table 1 lists radiocarbon ages for Aboriginal relics within these sites.

Site 1, at the southernmost end of the lunette, includes a human cremation and hearths containing burnt mammal, bird and fish bones, emu egg shell, shells and stone artefacts.

Table 2 Ethylene Production by Some Soil Isolates

Organism	Ethylene produced (p.p.m.)
Yeast 13G	136.0
<i>Mucor hiemalis</i>	21.1
Yeast 5H	19.9
<i>Penicillium</i> 13E	0.8
<i>Mucor</i> 13F	0.4
<i>Aspergillus</i> 13D	0.3
Bacterium 1C (gram variable coccus)	0.2
Bacterium 11C (gram positive rod)	0.1
Bacterium 3C (gram positive rod)	<0.1
Bacterium 10B (gram positive rod)	<0.1
Actinomycete 9B	<0.1

Pure colonies were grown on mineral salts-glucose-methionine agar slopes (10 ml.) in screw-capped bottles (30 ml.) and incubated at 25° C. All organisms grew to cover the surface of the agar. Ethylene was assayed by gas chromatography after 5 days. Uninoculated controls produced less than 0.1 p.p.m. ethylene.

The burial site and most of the hearths are within an ancient high water beach deposit, which is exposed for 300 m along the length of the eroding dune¹. Bowler *et al.*² discuss radiocarbon dates from the Mungo skeleton and a nearby hearth, and conclude that the age of the skeleton is between 24,500 and 26,500 BP. The ages of the remaining (undated) hearths are probably close to that of the skeleton.

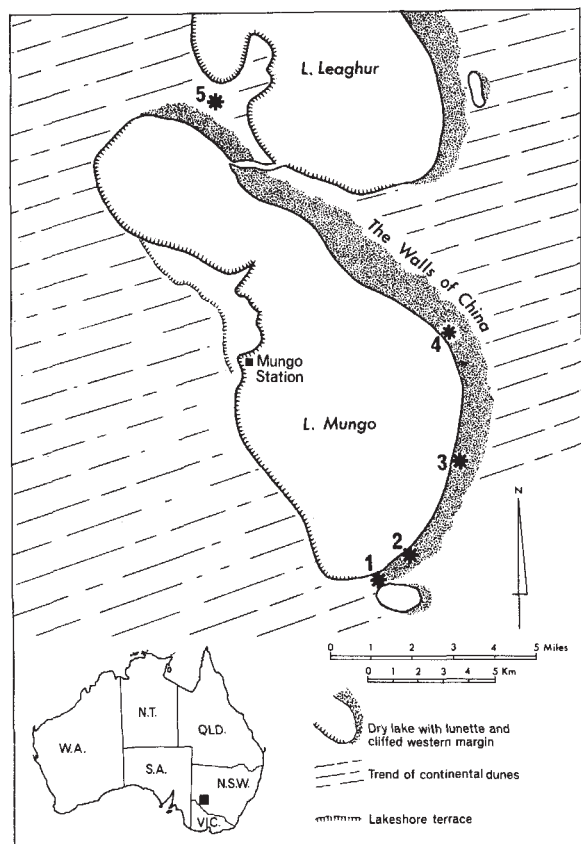


Fig. 1 Location of the archaeological sites at Lake Mungo (after Bowler *et al.*¹).

At site 2, 1.5 km north-east of site 1, Bowler found artefacts and unionid shells (*Velesunio ambiguus*) encrusted with secondary soil carbonate lying on an eroded surface cut into the Mungo unit¹. Some shells were found *in situ*, and were combined with shells from the deflation surface to give a radiocarbon age of $32,750 \pm 1,250$ BP (ANU-331, Table 1). The stone artefacts may possibly have eroded from an horizon immediately above that containing the shells; but even if

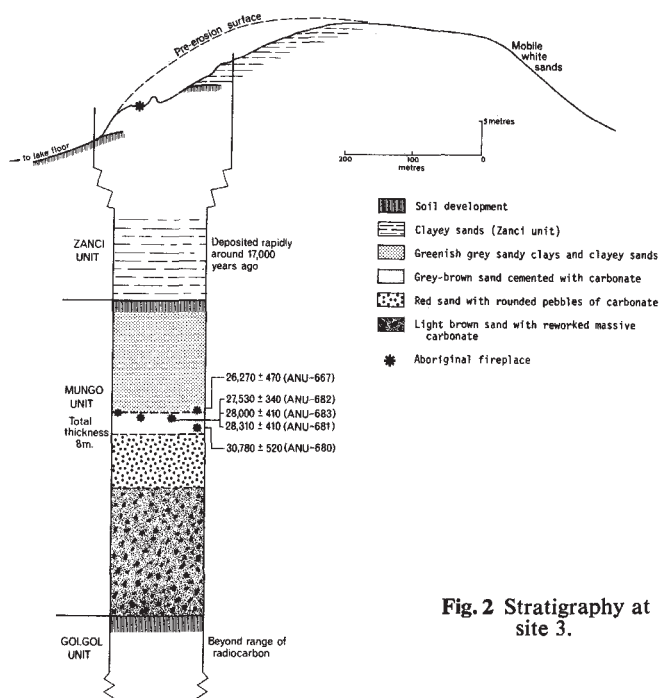


Fig. 2 Stratigraphy at site 3.

that were so, human transport seems the only likely explanation for the abundance of large unionid shells high in the lunette.

Site 3, 5.5 km north-east from the southernmost end of the lake, consists of a group of five Aboriginal fireplaces in an area about 4 m across which have provided a record of a major excursion of the Earth's magnetic field³. Fig. 2 shows the relationship of these fireplaces and the dune stratigraphy. The Golgol unit¹ is overlain by 3 m of light brown sand containing reworked angular fragments of massive carbonate. This is covered by 1 m of red sand, containing sparse rounded pebbles of carbonate (typically about 1 cm in diameter), which grades upwards into a thin bed (20 cm) of grey-brown sand, the top of which is marked by a clearly defined contact with a coarsely banded greenish-grey sandy clay which grades upwards into clayey sand upon which a pale yellow-brown soil has developed, marking the top of the Mungo unit. The thinly-bedded aeolian clayey sands of the Zanci unit¹ complete the stratigraphic column.

The grey-brown sand horizon extends for several hundred metres north of site 3, and contains numerous remains of fires, and occasionally stone artefacts and burnt emu egg shell; however, at site 3 itself neither artefacts nor food remains have yet been found. The abundant traces of occupation, the range of about 4,000 years in the radiocarbon ages of the fireplaces, and the sharp upper contact of this horizon

Table 1 Radiocarbon Ages from Lake Mungo

Site	Reference	Laboratory No.*	¹⁴ C age yr. BP	Material dated	Comment
1	Bowler <i>et al.</i> ²				Age of Mungo skeleton $25,500 \pm 1,000$ BP Adjacent hearths have similar age
2	Bowler <i>et al.</i> ¹	ANU-331	$32,750 \pm 1,250$	Shell	Unionid shells with stone artefacts
3	Barbetti and McElhinny ³	ANU-667	$26,270 \pm 470$	Charcoal	Oven at base of greenish-grey clay
		ANU-680	$30,780 \pm 520$	Charcoal	Oven in grey-brown sand
		ANU-681	$28,310 \pm 410$	Charcoal	Hearth at top of grey-brown sand
		ANU-682	$27,530 \pm 340$	Charcoal	Oven at top of grey-brown sand
		ANU-683	$28,000 \pm 410$	Charcoal	Hearth at top of grey-brown sand
4	Polach <i>et al.</i> ⁴	ANU-303	$30,250 \pm 950$	Charcoal	Hearth in red, cross-bedded sands
5	Allen†	ANU-372A	$24,020 \pm 1,480$	Charcoal	Unionid shell midden with charcoal
			$-1,250$		
		ANU-372B	$27,160 \pm 900$	Shell	

* Radiocarbon Laboratory, Australian National University. † Unpublished data.

suggest that it was a loose sandy surface for a few thousand years before it was sealed beneath later sediments. Preliminary thin section analysis revealed some alignment of clay minerals towards its base and also in the underlying red sand, but the top part of the grey-brown sand showed no evidence of pedogenesis. This is consistent with the view that an occupied sandy surface would be constantly disturbed. Later, the sand was lightly cemented with calcium carbonate and sealed by the overlying greenish-grey clay.

The oldest fireplace (ANU-680, Table 1) at site 3 is a typical Aboriginal oven—a shallow depression filled with ash and pieces of charcoal, with several lumps of baked clayey sand arranged on top (these were used as substitute cooking stones in the Lake Mungo region). These ovenstones were oriented before excavation, and later archaeomagnetic measurements showed that the direction of their remanent magnetization was identical to that of samples of baked earth from underneath the floor of the oven³ demonstrating that the ovenstones had not been displaced. Charcoal sealed underneath the ovenstones was collected separately. Two charcoal samples were collected from parts of the oven not sealed by ovenstones, and all three radiocarbon analyses were in statistical agreement; they were therefore averaged to give a reliable age of $30,780 \pm 520$ BP (ANU-680, Table 1).

Two of the fireplaces (ANU-681, ANU-683, Table 1) at site 3 are hearths—small round areas of burnt and blackened earth about 30 cm diameter covered with ash and charcoal. Two of the ovens (ANU-667, ANU-682, Table 1) had been affected by recent erosion of the lunette, which had caused some displacement of the ovenstones. Reliable radiocarbon ages were determined from charcoal collected from undisturbed parts of these ovens.

Preliminary archaeomagnetic measurements on samples from one fireplace (ANU-682, Table 1) showed that their directions of magnetization were not as consistent as expected³. This unusual degree of scatter was also observed in samples from a contiguous fireplace (ANU-683, Table 1), suggesting that these fireplaces may have been superimposed on older fireplaces underneath. Additional samples are being collected for further study.

At site 4, 5 km north of site 3, Bowler found charcoal (ANU-303, Table 1) in red, cross-bedded sands of the Mungo unit⁴. Although contemporaneous with aeolian activity, the charcoal was found only in an elliptical area about 30 cm across, indicating that it was the undisturbed remains of a fire. Its size and shape suggest that it was an Aboriginal hearth (Bowler, personal communication).

Site 5 is located on a sandy ridge near the northernmost end of the Lake Mungo lunette, overlooking Lake Leagur. A unionid shell (*V. ambiguus*) midden about 10 m across in grey, thinly stratified sand contains numerous pieces of charcoal. Radiocarbon ages obtained from shell and charcoal from the upper layers of the midden are in statistical agreement (ANU-372, Table 1). During excavation, shells, fragments of bone and stone flakes were found as much as 1.2 m beneath the dated horizon, indicating human activity at an earlier time than the reported age.

The sites at Lake Mungo described here show that it was occupied 32,000 years ago. Moreover, there is considerable variation in the type of site. Site 4 is a single hearth, site 5 a specialized shell midden and site 1 an extensive camping site containing evidence of a number of human activities. The stone implements at the sites belong to the "Australian core tool and scraper tradition" and consist mainly of irregular steep-edged scrapers. Such tools were still in use in Australia when Europeans arrived.

Several other archaeological sites in Australia have provided evidence of man's presence before about 20,000 BP. Jones⁵ and Mulvaney⁶ have discussed radiocarbon dates from Australia. The oldest reliable evidence came from the Malangerr site in the Northern Territory (ANU-77B, $22,900 \pm 1,000$ BP)⁷ and from Koonalda Cave in South Australia

(ANU-245, $21,900 \pm 540$ BP)⁸. Both Jones⁵ and Mulvaney⁶ consider dates older than these, from the Lake Menindee archaeological site in western New South Wales (LJ-204, $26,300 \pm 1,500$ BP)⁹, from the Keilor archaeological site near Melbourne, Victoria (ANU-65, $31,600 \pm 1,300$ BP)¹⁰, and also from Koonalda Cave (V-82, $31,000 \pm 1,650$ BP)⁸, but conclude that additional detailed information of each site would have to be provided before these dates could be considered reliable^{5,11}. On the basis of the dates reviewed both Jones and Mulvaney concluded that Aboriginal man was probably in Australia before 30,000 years BP. Now, however, radiocarbon ages from new archaeological sites have been published. A campfire from Pleistocene Lake Yantara in north-western New South Wales has an age of $26,200 \pm 1,100$ BP (GaK-2121)¹² and the lowest level of the Burrill Lake rock shelter on the south coast of New South Wales has been dated at $20,760 \pm 80$ BP (ANU-137)¹³.

With the addition of the Lake Mungo evidence it is clear that during the period 25,000 to 32,000 BP man had learnt to exploit the diverse resources of coastal and inland regions of Australia, and had already adapted his basic stone industry to one which was to survive with little change for the next 25,000 years. Such successful adaptation to the environment suggests that he may have been in Australia considerably before 32,000 BP.

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Pleistocene Man in Australia: Age and Significance of the Mungo Skeleton

THE Late Pleistocene human cremation found at Lake Mungo in western New South Wales is among the most significant recent discoveries in Australian prehistory¹. The fragmented skeleton of this young, adult female² was recovered from a

buried soil on the Lake Mungo shoreline dune (lunette) known as "The Walls of China" (see accompanying paper, site 1). This paper records new radiocarbon data providing a precise age for these remains.

The human bones were exposed in the calcreted horizon of the Mungo unit from which the overlying Zanci aeolian sediments³ had been stripped by erosion (Figs. 2, 3). Before terminal burial in a shallow grave the body had been burnt and the resulting charred bones extensively smashed. Reconstruction of the cranium shows the Mungo female to be fully sapient, lying not only "within the range of recent Australian skeletal form", but "at the morphologically modern end" of that range².

As the remains were discovered during a study of surficial geology and Quaternary stratigraphy of lake deposits, age limits were determined from ¹⁴C dates of sediment elsewhere within the Mungo unit. Charcoal from a probable hearth 10 km north of the burial site located in brownish red Mungo sands yielded a ¹⁴C age of $30,250 \pm 950$ BP (ANU-303). Unionid shells from a deflation surface cut into the same unit 1.5 km north-east from the burial were dated at $32,750 \pm 1,250$ BP (ANU-331).

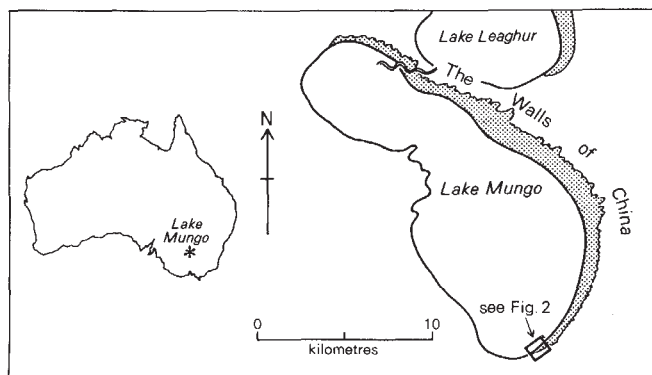


Fig. 1 Location diagram showing site of human remains, Lake Mungo.

After reconstructing stratigraphic detail in the eroded dune at the burial site, and arguing from the regional analysis, Bowler estimated the age of the remains as being "between 25,000 and 32,000 BP"¹. This estimate implied the skeleton was up to 10,000 years older than any other human remains previously dated in Australia. In the absence of any ¹⁴C dates from the burial site, however, the age and therefore the significance of the bones remained in doubt.

Direct dating from the burial region now provides a definitive estimate of age (Table 1). This involves ¹⁴C determination of charcoal from a hearth stratigraphically equivalent to a level 15 cm above that of the burial, and dating of "collagen" and bone apatite from skeletal fragments.

A sediment sample (ANU-375) was obtained from one of many small concentrations of burnt organic matter within calcareous sediment exposed on the deflation surface 40 m east of the burial site along the strike of dipping lakeshore beds (Fig. 2). By trenching and precise levelling, equivalent soil and sedimentary horizons between the burial and hearth sites were identified and correlated to within a few centimetres to produce a complete sequence (Fig. 3). In this way, the equivalent level of the ¹⁴C sample was fixed at about 15 cm above the surface of the calcreted bones. Sediments containing the hearth were therefore the same age as those into which the grave was cut and by which it was later covered. The hearths, of which ANU-375 is representative, were cut into a horizon representing an ancient high water beach deposit. They included charcoal, stone artefacts and burnt animal bone¹, distributed in an arcuate zone representing the remnants of ancient shoreline camp sites.

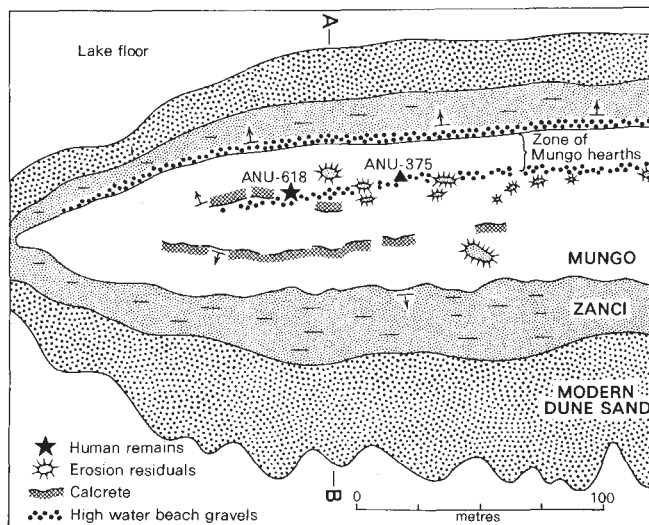


Fig. 2 Plan of lunette stratigraphy showing location of human remains and their relationship to zone of strandline occupation from which ¹⁴C sample (ANU-375) was obtained.

Carbon in the sample occurred in three forms. First, charcoal pellets were associated with finely dispersed black, charred remains of plant materials from a local fire. Second, the small sand-sized lacustrine carbonate, consisting mainly of comminuted shell fragments, formed a small percentage (less than 10%) of the sedimentary population. Third, the deposit was weakly cemented by secondary carbonate associated with soil development in the Mungo unit. It formed part of the buried calcrete (Bca) horizon in which the skeletal remains were located. Age determinations are available from two fractions: plant-derived organic carbon, and acid soluble total carbonate.

Table 1 Radiocarbon Dates in Years BP relating to Age of the Mungo Skeleton

ANU-331	$32,750 \pm 1,250$	Unionid shells at lakeshore dune 1.5 km NE of Mungo site; believed to have been transported by human agency ^{3,4} .
ANU-303	$30,250 \pm 950$	Charcoal from suspected hearth dug into red cross-bedded sands on Walls of China approximately 10 km N of Mungo site ⁴ .
ANU-375A	$20,280 \pm 280$	Carbonate (90% soil carbonate) from beach sands in which charcoal of ancient aboriginal hearth is located. From 40 m E of human remains.
ANU-375B	$26,250 \pm 1,120$	Charcoal fraction from hearth stratigraphically equivalent to 15 cm above human remains. Age represents occupation on lake shore synchronous with human burial.
ANU-618A	$19,030 \pm 1,410$ $1,200$	Carbon dioxide from human bone derived from acetic acid insoluble fraction, "bone apatite".
ANU-618B	$24,710 \pm 1,270$ $1,100$	HCl insoluble residue ("collagen" fraction) of Mungo skeletal remains.

Following their removal from the Mungo site, the human remains were extracted from the calcrete block by A. G. Thorne for anatomical reconstruction. A sample of the charred bone (ANU-618) comprising small unidentifiable post-cranial fragments was used for ¹⁴C analysis.

After acetic acid leaching under vacuum to remove encrusting soil carbonate, the residue was reacted with hydrochloric acid and the evolved CO₂ used for measuring ¹⁴C activity. The resulting date is reported as representing the apatite component⁵. The acid insoluble residue was dried and burnt to yield the final CO₂ fraction reported as the "collagen" date.

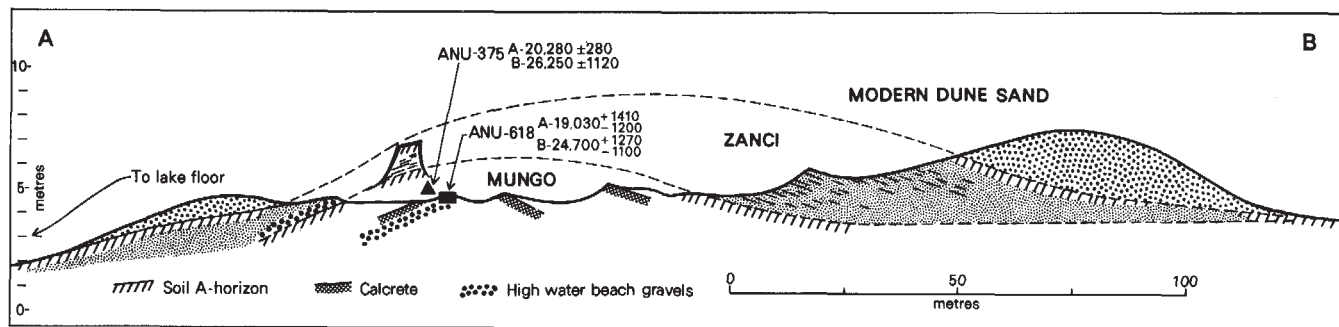


Fig. 3 Section through A-B (Fig. 2) showing stratigraphic relationship between human remains (ANU-618) and adjacent radiocarbon sample (ANU-375).

Of the various fractions dated, the charcoal (ANU-375B) is less susceptible to chemical exchange with contaminating carbon than is carbonate or apatite. Moreover, in this environment contamination by post-depositional organic accumulation is not a hazard. The charcoal date therefore accurately represents the age of the hearth. In doing so, it also dates the beach sediments into which the hearth was cut and which formerly overlaid and sealed the grave. The ^{14}C age of the hearth is therefore closely related to the age of the burial.

In the bone sample (ANU-618B) the effect of burning was to retain a higher proportion of organic carbon than would otherwise be preserved. Acid insoluble residues from such samples give more reliable ages than those from uncharred bone samples⁶. The resulting date ($24,710 \pm 1,100$ BP) is in statistical agreement with that derived from hearth charcoal ($26,250 \pm 1,120$ BP). Both overlap within the range $25,500 \pm 1,000$ BP; the age of the burial therefore lies within this range.

Although the carbonate and apatite fractions are subject to more active ^{14}C exchange than is organic carbon, the ages they provide are consistent with the pattern of the ^{14}C variability within secondary carbonate in this environment. A controlled study of the ^{14}C content of pedogenic carbonates⁷ suggests that soil carbonate in this semi-arid environment has an activity reflecting an age which is younger than that of the sediment on which it is formed and close to the true age of pedogenesis.

At the Mungo site, burial of the Mungo soil by Zanci sediment ranges from 17,500 BP to about 20,000 BP; soil formation on the Mungo unit is therefore restricted to that period between the ^{14}C age of hearth charcoal and the beginning of Zanci deposition. The ^{14}C carbonate age falls neatly between the two, suggesting it represents the actual age of pedogenesis at the site.

The ^{14}C discrepancy between the bone apatite and collagen fractions remains to be explained. X-ray analysis of Mungo bone after acetic acid leaching confirms that the only carbonate mineral present is apatite structurally resembling dahllite. The higher activity of carbon derived from this fraction must therefore be ascribed to exchange with soil bicarbonate in the ionic state. The close agreement between the ^{14}C results derived from soil carbonate and bone apatite supports this view.

The new radiocarbon data define the age of the Mungo remains as lying between 24,500 and 26,500 BP. Both the stratigraphic evidence and ^{14}C analyses of the hearth charcoal and charred bone provide a consistent age control.

Moreover, the data establish the age of high levels in Lake Mungo with which occupation was associated. At 26,000 BP this lake contained water to a depth of more than 8 m, although like others in the region it has been dry for the last 15,000 years². The "pluvial" environment exploited by its shoreline inhabitants at the time of the Mungo cremation was very different from that today. The high water phase was followed by a low oscillation which is correlated with soil formation on the Mungo sediments. The carbonate dates are consistent with this later event having occurred between 23,000 and 19,000 BP.

The major significance of these dates, however, lies in the accurate control they provide for the age of the human remains. A number of Australian fossil specimens have pointed to the presence of morphologically modern people on the continent towards the end of the Pleistocene period. This has been supported by osteological evidence that Tasmania was occupied, certainly by 8,000 BP⁸, by Aborigines who were closely allied physically to the modern mainland population⁹. The Lake Mungo remains, which exhibit modern Aboriginal form², confirm this information and greatly extend it chronologically. This cremation disposal demonstrates that modern physical form has been maintained in south-eastern Australia for at least the last 26,000 years.

Further, the Pleistocene presence of a late sapiens morphology in southern Australia has important implications for south-eastern Asia, if the migrational source for modern Australians is to be found in that region. Given the time required for genetic infiltration and/or migration, sufficient to traverse the Malayo-Indonesian area and to cross north Australia, the presence of a morphologically modern people in the Murray Basin by 26,000 BP at the latest argues for the much earlier presence of similarly modern groups on the south-east Asian mainland. This is supported by the morphology and probable age of the Niah skull¹⁰. The Lake Mungo skeleton suggests that fully sapient populations were present in south Asia earlier than their known presence elsewhere.

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Convulsive Properties of d-Tubocurarine and Cortical Inhibition

THAT d-tubocurarine (DTC) is convulsant when applied topically to the cerebral cortex has been known for many years but the mechanism of its action is still unclear¹⁻³. Other neuromuscular blocking drugs such as gallamine, decamethonium and dihydro- β -erythroidine do not have this convulsive property⁴ and the usual comparison is with known convulsants such as picrotoxin and strychnine^{1,4,5}. This suggests that different receptors to those in the periphery are involved in the convulsive action of DTC and it is possible that the central receptors with which DTC interacts may be those mediating cortical inhibitory processes. Blockade of these receptors would result in uncontrolled excitation and lead to paroxysmal discharges. As γ -aminobutyric acid (GABA) is now thought to be the cortical inhibitory transmitter⁶, we have examined the interactions of DTC and GABA, applying both substances by microiontophoresis. In addition we have studied the effects of microiontophoretically applied DTC on the inhibition of cortical neurones produced by direct shocks to the adjacent cortical surface^{7,8} and we have also compared DTC with other convulsants applied to the same neurones, from the same pipette.

Seven barrelled glass micropipettes containing d-tubocurarine chloride (5 mM, aqueous solution), γ -aminobutyric acid (0.2 M, pH 3.5), bicuculline (5 mM, 165 mM NaCl, pH 3.5), picrotoxin (5 mM, 165 mM NaCl) and sodium glutamate (0.2 M, pH 8) were prepared as described previously⁹. Drug ions were applied by conventional microiontophoretic techniques to neurones between 600 and 1,600 μ m deep in the suprasylvian gyri of nine cats lightly anaesthetized with N_2O /halothane. Where neurones were not firing spontaneously they were driven by application of glutamate.

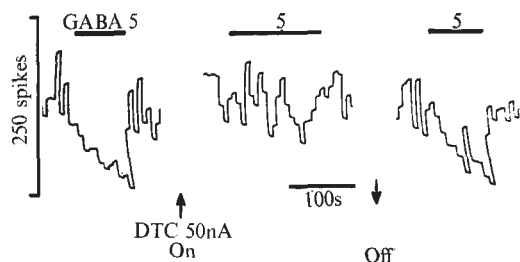


Fig. 1 Spike counter record of the firing of a feline neocortical neurone driven by continuous application of 10 nA glutamate. GABA 5 nA was applied where indicated by the bars above the trace. DTC 50 nA was applied continuously between the arrows beneath the trace. 2 min after commencing the application of DTC, the depressant effects of GABA were negligible (centre trace), although there was no significant change in base line firing rate. 30 s after terminating the application of DTC the depressant response to GABA had recovered.

DTC consistently and potently antagonized the depressant effects of GABA on 20 of the 28 neurones studied (Fig. 1). On most of the cells studied, DTC also produced a pronounced increase in firing rate. Antagonism of GABA could be seen, however, in the absence of any large change in firing rate (Fig. 1), and in every case we have studied the depressant response to GABA was recovered before the firing rate fell towards control levels. In comparison to bicuculline and picrotoxin¹⁰, DTC was effective with much smaller expelling currents (10 to 25 nA), although this does not imply that DTC was active at lower extracellular concentrations than the other two drugs.

When tested against inhibition produced by direct cortical stimulation⁸ the effects of DTC were less clear cut. In four of the seven neurones studied there was a small reduction in the

inhibitory period following the stimulus; in two there was no discernible effect, and in one the inhibition was slightly prolonged. The reduction in inhibition could also be obtained when there was no pronounced increase in firing rate (Fig. 2). The effects on neurally evoked inhibition are comparable with those obtained by other workers using iontophoretically applied bicuculline¹¹ and rather better, in terms of reducing the inhibitory period, than those we ourselves currently obtained with iontophoretic bicuculline and picrotoxin.

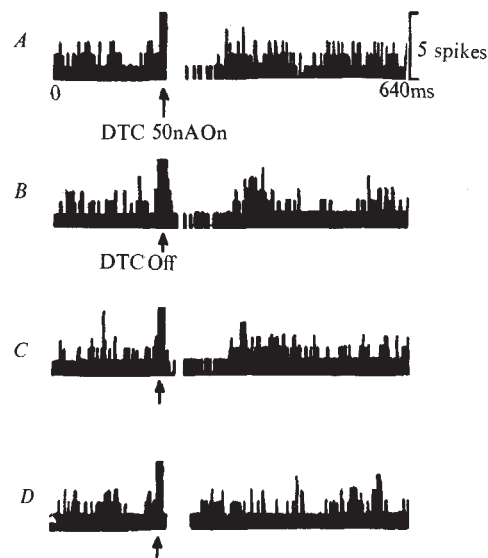


Fig. 2 Computer generated spike density histograms of the firing of a second neocortical neurone; stimuli (0.25 Hz, single pulses 0.2 ms wide, 4 V) were applied to the adjacent cortical surface via a monopolar silver ball electrode. Spike firing was accumulated in 1,000 sequential stores during 30 consecutive sweeps of 640 ms duration. The stimulus was triggered (indicated by vertical arrows) 200 ms after the start of the computer sweep. The large count associated with the stimulus in each case represents the stimulus artefact. Histogram A was a control record, and in between A and B DTC 50 nA was turned on. Four minutes later (B) the inhibitory period was reduced and some early excitation was noticeable. DTC was then turned off and one minute later histogram C was plotted showing that the inhibition was still reduced although the early excitation had been lost. Two minutes later (D) the inhibitory effects of surface stimulation had fully recovered. During the application of DTC to this unit the depressant effects of iontophoretic GABA were very much reduced.

We have had difficulty in obtaining satisfactory depression of firing of cortical neurones using glycine¹⁰ but where comparative studies have been possible DTC appears to antagonize both GABA and glycine depressions. This might be taken as evidence that DTC lacks specificity though it is worth noting that bicuculline has now been shown to antagonize both GABA and glycine when tested in the rat cerebral cortex, but will show specificity in antagonizing GABA when tested in the spinal cord¹².

Previous reports⁸ that DTC shows no interaction with direct cortical inhibition or with GABA depressions can possibly be accounted for by the small number of neurones actually tested and the use of supramaximal inhibitory stimuli. In one case the DTC was given intravenously and the quaternary ammonium grouping of DTC¹³ makes it unlikely that any actually entered the CNS.

We suggest that the convulsant action of DTC is due, at least in part, to its antagonism of the inhibitory influence of endogenous GABA. This idea is consistent with the observation that topically applied DTC has 5 to 10 times the convulsive potency of strychnine on the cortex^{4,5}, strychnine being a poor GABA antagonist at this site¹⁴. However, it appears likely that the increase in firing rate produced by DTC

is not caused solely by disinhibition since we can dissociate the antagonism of GABA from the increase in firing rate due to DTC*.

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* Inhibition of acetylcholine-mediated pathways is less likely to explain the convulsive action of DTC since other antagonists of acetylcholine are not convulsant⁴.

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Electrochemical Measurements of Blood Alcohol Levels

THE measurement of alcohol concentration in the breath is a more convenient and desirable method of enforcing the drinking and driving laws than the collection and analysis of blood samples. This method is valid because the alcohol concentration in alveolar air is proportional to the alcohol concentration in the blood; it is essential to ensure that the breath sample contains only alveolar air^{1,2}.

The present methods of analysing the breath sample are based on the colour change of potassium dichromate when reduced by alcohol and this principle is used as a screening device^{3,4} and as an evidential device^{2,5,6}. The screening device used in Great Britain is subject to large errors and a blood analysis is also required for conviction in a court of law. The data obtained with the spectrophotometric devices may be used as evidence in many states in the USA, in Canada and in Australia but, because of their operational complexity, their size and their use of chemicals (which must be disposed of after use), they are not suitable for use in police cars.

Here we describe a technique for the measurement of alcohol concentration in the breath which is more accurate than the present evidential devices and yet is portable and simple to operate so that it may be used at the scene of a traffic offence. Thus it can be considered for use either as a screening or as an evidential instrument.

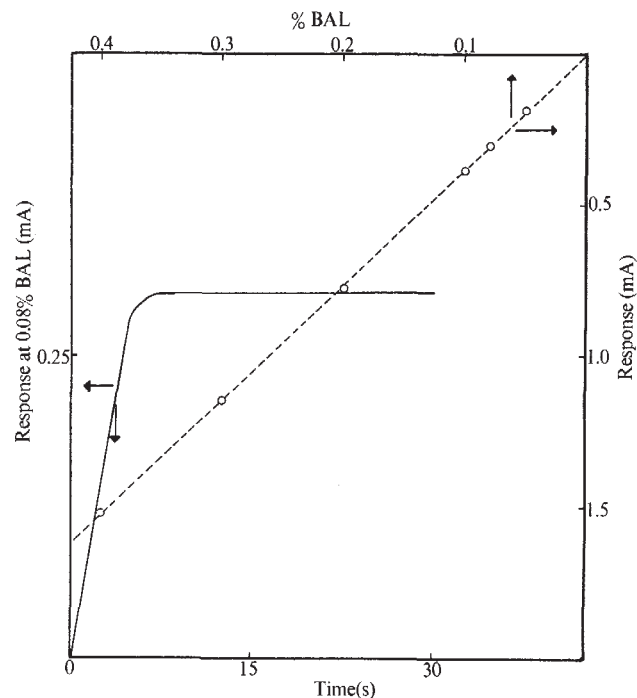


Fig. 1 Response as a function of time and % blood alcohol level (BAL).

The analysis is based on the electrochemical oxidation of alcohol in a breath sample at a potential controlled electrode. This electrode potential is maintained in a region where neither the reduction of oxygen (a cathodic process) nor the oxidation of water (an anodic process) occurs at an appreciable rate. Alcohol is electro-oxidized to acetic acid via acetaldehyde as an intermediate in a 4 electron process in this potential region⁷ and the current associated with this electrochemical process is measured.

The detector cell contains an anode, a counter electrode and a reference electrode with concentrated sulphuric acid solution as the electrolyte. A constant potential difference is applied between anode and reference electrode by a potentiostat so that the anode is maintained at a potential within the range of 0.9 V to 1.5 V versus a reversible hydrogen electrode. The anode and counter electrode are 'Teflon'-bonded, platinum diffusion electrodes⁸. The breath sample is passed over the back (gas side) of the anode at constant flow rate. The alcohol diffuses to the electrocatalytic surface where it is oxidized and the current flowing between the anode and counter electrode is measured. This diffusion limited current is proportional to the partial pressure of alcohol in the breath. The kinetics of electro-oxidation of alcohol to acetic acid are not limiting under these conditions of operation.

During the operation of the instrument, the subject breathes into a heated chamber from which the sample is passed to the detector cell. The signal generated is displayed on a d.c. meter which is calibrated in terms of the blood alcohol concentration. The temperatures of the reservoir, of the cell and of the connecting tube are maintained above body temperature to prevent any change occurring in the ethanol partial pressure between the exhalation of the breath sample and its oxidation in the electrochemical cell.

To obtain a true alveolar sample, the volume of expired breath must be greater than 1 l. The instrument automatically indicates when 1.2 l. of breath has been exhaled through the instrument, and only the last portion of the alveolar air is retained for analysis.

Fig. 1 shows a typical curve of signal versus time elapsed from admittance of sample for a sample equivalent to a blood alcohol content of 80 mg of alcohol/100 ml. of blood. It is seen that the steady state current is obtained in 6 s, thus

permitting rapid analysis. Fig. 1 also shows the cell steady state response *versus* blood alcohol content. These data were obtained using a simulated "breath" sample prepared by passing air through standardized alcohol solutions. This plot is linear up to a blood alcohol content of 400 mg of alcohol/100 ml. of blood which is the highest value investigated. The signals at any given alcohol concentration were reproducible in consecutive duplicate tests within ± 2 mg of alcohol at blood alcohol levels of 200 mg/100 ml., and within ± 10 mg of alcohol at blood alcohol levels of 400 mg/100 ml. This duplication of results is well within the limits recently suggested for a breath testing device².

Over 2,500 tests have been run on one of the detector cells using simulated breath samples. The standard deviation of the measured alcohol concentration on the breath from the solution alcohol concentration was 3 mg of alcohol over a range of blood alcohol levels of 50 mg/100 ml. to 200 mg/100 ml., values significantly more accurate than the colorimetric alcohol detectors and well within the evidential requirements for breath alcohol measurements^{2,5}. It is, in fact, better than the standard deviation observed with blood analysis⁵.

Calibration checks of individual sensor cells over a period of 4 months' operation and 2,500 tests show only minor changes in signal (3% reduction per month). Thus a monthly calibration check would be adequate for a roadside screening device. The formation and build-up of acetic acid in the strong acid electrolyte have no influence on the cell response (and hence on the kinetics of alcohol electro-oxidation) over 2,500 tests.

Our studies with this instrument indicate that the electrochemical oxidation of alcohol is a more accurate technique for the measurement of alcohol in breath samples than the instruments based on colorimetric methods of detection. The electrochemical detector cell may be built into a rugged, portable unit which may be used by a police officer at the scene of a traffic offence either as a screening instrument or as an evidential device.

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Active Transport of Lysergic Acid Diethylamide

ALTHOUGH it is recognized that there is little hindrance to the passage of lysergic acid diethylamide (LSD) across the blood brain barrier¹, an autoradiographic study of LSD distribution in the rat brain led to speculation that the choroid plexuses are involved in the active transport of this compound between blood and cerebrospinal fluid². It was also suggested that this tissue acts as a storage site for LSD in the brain. The purpose of this communication is to elucidate the mechanism

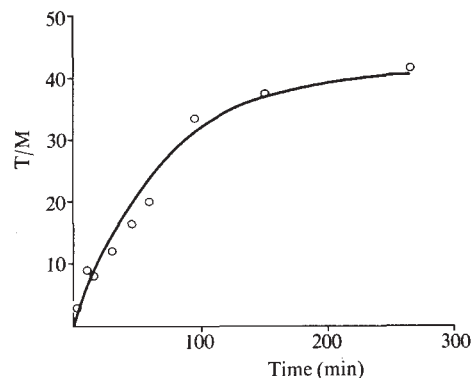


Fig. 1 Accumulation of ³H-LSD by the frog choroid plexus with time. Uptake is expressed as the T/M ratio.

of LSD accumulation within the choroid plexus, and clarify the role of the choroidal epithelium in the distribution of LSD between blood and brain.

I used an *in vitro* preparation of a choroid plexus to measure (i) unidirectional fluxes across the epithelium, and (ii) accumulation within the epithelium from the solutions bathing the ventricular and/or vascular surface of the tissue^{3,4}. The posterior choroid plexus was removed from bullfrogs (*Rana catesbeiana*) and LSD accumulation within the plexus was measured during incubation in 3 ml. of physiological saline containing ³H-LSD. The tissue was then rinsed in saline, drained of surface fluid, weighed and dissolved in tissue solubilizer. The total radioactivity in the tissue was determined by liquid scintillation counting and uptake was expressed as the T/M ratio:

$$\frac{T}{M} = \frac{\text{concentration of LSD per ml. of tissue water}}{\text{concentration of LSD per ml. of incubation media}}$$

To measure the unidirectional fluxes of ³H-LSD across the choroid plexus the tissue was mounted in between two lucite half chambers. A tracer quantity of isotope was added to the solution on one side of the plexus and the rate of appearance of the isotope in the "cold" solution on the opposite side was measured. At the conclusion of the experiment the amount of isotope in the plexus was determined as outlined above. In a few experiments ³H-LSD was added to both the ventricular and the serosal solutions, and after equilibration with the tissue the external solutions were changed rapidly, and the efflux of isotope from the plexus was measured by sampling the ventricular and serosal solutions at regular intervals. Unidirectional fluxes are expressed in mol/cm²/h and the uptake from the ventricular or serosal solutions is expressed in mol/cm². All errors are quoted as the standard error of the mean with the number of estimates in parentheses.

Experiments were carried out mostly at room temperature (22–24° C) in a physiological saline containing 85 mM NaCl, 2 mM KCl, 1 mM CaCl₂, 1 mM MgSO₄, and 25 mM NaHCO₃ gassed with 95% O₂–5% CO₂. ³H-LSD (New England Nuclear Corp., lot number 281–190) had a specific activity of 1.9 Ci/mmol and its radiochemical purity was greater than 93%. The purity was checked by thin-layer chromatography on silica gel plates using ethanol:acetic acid:chloroform (10:2:18). In all experiments the final concentration of LSD in the physiological saline was 3 μM, which is in the concentration range used to produce psychological effects. In general experimental procedures were as described before⁵.

Fig. 1 shows the time course of ³H-LSD accumulation. The T/M ratio increased rapidly during the first few minutes and thereafter more slowly, reaching a steady state after about 3 h. There was no indication of instantaneous binding of LSD to the tissue. The steady state T/M ratio was 45 ± 3 (12). As Fig. 2 shows, the accumulation of LSD within the plexus was reduced by 65% in the presence of ouabain (1.5×10^{-5} M), iodoacetate/cyanide (3 mM) and by low temperature (0° C).

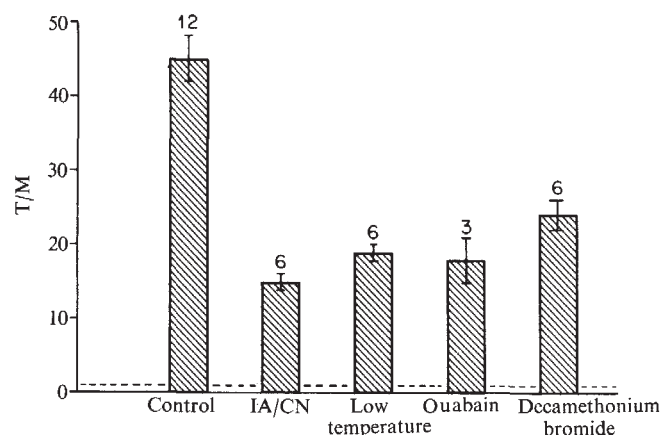


Fig. 2 Effect of inhibitors on ^3H -LSD accumulation by the choroid plexus. The T/M ratios were obtained after 2.5 h incubation in the physiological saline, (i) at room temperature (control), (ii) at 0°C , (iii) with 3 mM iodoacetate/cyanide (IA/CN), (iv) with 1.5×10^{-5} M ouabain, and (v) with 1 mM decamethonium bromide. The T/M ratio corresponding to a simple passive distribution of the LSD between the medium and tissue water is indicated.

Furthermore, the quaternary ammonium compound, decamethonium bromide (1 mM), reduced the uptake of LSD by 50%.

The ^3H -LSD was accumulated equally well across either the ventricular or the serosal surface of the plexus; in the steady state the uptake from the serosal solution corresponded to 13 ± 1 (6×10^{-10} mol/cm 2 (T/M ~ 3), whereas the uptake from the ventricular solution corresponded to 22 ± 1 (5×10^{-10} mol/cm 2 (T/M ~ 5). This was in sharp contrast to the amino-acids which were actively accumulated only across the ventricular surface of the tissue⁵.

Two procedures were used to establish the state of the ^3H in the plexus. (1) After equilibration of the tissue with ^3H -LSD in the external solutions, the efflux of isotope into the ventricular and serosal solutions was measured. More than 75% of the accumulated isotope was free to wash out into the ventricular and serosal solutions. This again contrasts with the amino-acids which washed out into the ventricular solution⁵. The fact that the serosal unstirred layer is effectively much thicker than the ventricular unstirred layer⁴ probably accounts for the difference in the amount of isotope washed out into the two solutions. (2) In two experiments the radioactivity in the choroid plexus was extracted by sonication in methanol. Thin-layer chromatography revealed that more than 80% of the tritium migrated as a single spot corresponding to ^3H -LSD, and that the remainder stayed at the origin. This suggests that 80% of the ^3H accumulated within the choroid plexus was free ^3H -LSD and that the remainder was bound to tissue proteins.

Unidirectional flux experiments showed that there was no significant net flux of ^3H -LSD across the choroid plexus in the absence of concentration gradients. The fluxes from ventricle to serosa and from serosa to ventricle were 0.18 ± 0.02 (30) and 0.17 ± 0.02 (34×10^{-9} mol/cm 2 /h respectively. Four experiments on the effect of iodoacetate/cyanide were inconclusive. In all four experiments there was a slight increase in the apparent unidirectional fluxes when the inhibitors were added. This apparent increase in flux resembles the effect of ouabain on potassium unidirectional fluxes across this tissue⁶ and in both cases it is probably a reflexion of the decrease in the intracellular concentration of the isotope. The unidirectional ^3H -LSD fluxes corresponded to a permeability coefficient of 1.5×10^{-5} cm/s—about a factor of five greater than the permeability of the neutral amino-acids. Similar experiments also showed that LSD was not actively transported across the arachnoid membrane.

It can be concluded from these experiments that ^3H -LSD is accumulated within the frog choroid plexus. Both the efflux experiments and the chromatographic analysis of the tissue

radioactivity indicate that more than 75% of the tritium accumulated within the tissue occurs as LSD not irreversibly bound to the tissue. A small percentage of the isotope in the plexus, however, does seem to be bound to some cellular components. These results are consistent with findings that LSD was metabolized to a significant extent only in the liver¹ and that a fraction of ^3H -LSD was firmly bound to the rat choroid plexus².

The absence of a significant difference between the unidirectional ^3H -LSD fluxes across the choroid plexus makes it unlikely that this amine is actively transported across the choroidal epithelium. It is more probable that the permeability of the tissue to LSD is sufficient to account for the rapid exchanges of this drug between the blood and cerebrospinal fluid. Choroid plexuses also do not seem to be well suited as storage sites for LSD in the brain since (1) the drug is accumulated equally well from the ventricular and serosal solutions, and (2) LSD accumulated within the choroid plexus does not preferentially wash out into either the ventricular or the serosal solutions.

^3H -LSD is accumulated within the frog choroid plexus by a process characteristic of active transport. Accumulation occurs against considerable concentration gradients (T/M=45) and depends on the supply of metabolic energy. The effect of ouabain (Fig. 2) suggests that a Na/K ATPase is directly or indirectly involved. There is much in common with the active accumulation of other amines in the choroid plexus. Primary amines (5-hydroxytryptamine and noradrenaline⁷), tertiary amines (narcotic analgesics^{8,9} and atropine¹⁰) and quaternary amines (hexamethonium, decamethonium and choline^{11,12}) are all actively accumulated within choroid plexuses. Kinetic studies have established that these amines share a common transport mechanism, that is, quaternary amines competitively inhibit the active accumulation of primary and tertiary amines. In the work reported here I have shown that the active accumulation of LSD was inhibited by the quaternary amine, decamethonium bromide. This suggests that the amine carrier in the choroid plexus is responsible for the active accumulation of LSD. Finally, on the basis of these results it is quite reasonable to speculate that LSD interacts with similar amine carriers and receptor sites in other cells and tissues such as those in the kidney and cerebral cortex. To assess the importance of such interactions in the hallucinogenic activity of LSD it will be necessary to measure the relative affinity of "receptor sites" in the central nervous system for LSD and the naturally occurring amines.

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BOOK REVIEWS

Alternatives to Eyes

Visual Prosthesis. Edited by T. D. Sterling, E. A. Bering jun., S. V. Pollack, and H. G. Vaughan jun. Pp. xviii+382. (Academic: New York and London, April 1971.) \$18.50; £8.65.

Visual Prosthesis contains the papers and discussion of the Second Conference on Visual Prosthesis held in Chicago in 1969 and also summarizes the First Conference of 1966 in an appendix.

Blindness is a human predicament resulting in a much greater dependence upon other people, the two particular problems being reading and mobility. Braille, the talking book, the long cane and the guide dog are current, but unfortunately limited, answers to these problems. This conference was convened to take a longer view and consider complete replacement of vision. This might be achieved through evoking phosphenes, the sensation of light elicited by direct stimulation within the visual pathways of the brain, or by using sophisticated techniques for stimulation of the skin.

The problem can be divided into two halves; that of processing the optical information to render it suitable for display and that of displaying it to the skin or the brain. Inevitably most interest centred on the experiments of Brindley who implanted an array of electrodes on the surface of the occipital cortex in a blind volunteer. In addition to the important scientific results on the nature of the phosphenes produced, questions of medical ethics were discussed. One participant thought such experiments could not yet be performed in the USA.

Many simulations have been performed to find out such things as how many display points would be needed for mobility and for reading. Considerable processing has taken place by the time signals reach the cortex in the visual system and various schemes of substitution for this preprocessing were considered. Against the need for extra processing Bach-y-Rita reported that good results could be obtained, with tactile stimulation using a simple imaging of the optical input with

camera control in the hands of the subject. Relatively little space is devoted to devices employing skin stimulation; as well as the work of Bach-y-Rita, sections are included describing a reading aid by Bliss, and a mobility aid by a group of Polish workers.

Rather surprisingly some of the blind members of the conference expressed the view that they would not welcome an ideal prosthetic device of the type envisaged. A man who is making a success of his life in spite of blindness does not want to have to start learning all over again, and the scientist should not necessarily assume that his attentions will be welcomed. The direct reporting of the discussions gives the reader a strong personal involvement, although the transatlantic telephone conversation with Brindley, who was not present at the conference, might have been better edited. J. P. WILSON

Better than Cure

Preventive Medicine. (An International Journal devoted to Practice and Theory.) Ernest L. Wynder, Editor-in-chief. Pp. 286. (Academic: New York and London, March 1972.) \$35.00 four issues (for institutional subscribers).

THE editorials of this issue are learned and interesting and, although some tautology is inevitable amongst seven authors writing on the same subject, these are valuable reference articles.

The aim of *Preventive Medicine* is to stress the application of existing knowledge without necessarily referring to why a treatment works. The problems mentioned are drug addiction, including alcohol, population control, accidents (and seat belts), nutritional problems, particularly obesity, and air and water pollution.

This issue is given over principally to coronary heart disease and its predisposing causes. One interesting and very unusual paper gives not only advice on recommended foods in CHD, but even includes a list of recipes.

Cardiovascular disease and cancer are less common in Japan than in the US, but as they approximate to the US

level in the Japanese who live in US it reminds us that such diseases are the product of man's own downfall, particularly by his dietary habits and smoking.

Preventive Medicine is welcome if only to combat "... medicine's long preoccupation with the retrieval of catastrophic disease...". Economics are barely mentioned, although a French nephrologist found that if everyone needing a kidney machine had one this would represent 80 per cent of the total security budget. It is necessary to consider whether one person should have a heart transplant or 5,000 have spectacles and dentures.

An article on the early detection of cancer of the cervix and breast brings us out of the cloud-cuckoo-land of the saving of life by early detection: it is, as another editorial states, the quality of remaining life which is so improved; if a person has a fatal cancer he should be a hedonist.

To sum up, the articles are generally excellent reviews, but the summaries are disappointing, and it is difficult to see what is the place of this journal and who will read it. The private doctor has not the time to read learned discussions and weigh statistical evidence; he needs experts to advise him. Should he need to know more he can turn to the specialist journals where the original work was published.

J. P. W. HUGHES

Atomic Theory

Molecular Reality: a Perspective on the Scientific Work of Jean Perrin. By Mary Jo Nye. Pp. xi+201. (MacDonald: London; American Elsevier: New York, February 1972.) £5.

THIS book was almost inevitable, although it is nonetheless welcome for that. The last decade has witnessed a spate of scholarly books and articles about the Daltonian atomic theory, its origins, the difficulties it encountered and its implications for the history of chemistry in general. No longer is it possible (if indeed it ever was) to overlook the grave setbacks that chemical atomism received within half a century

of its birth. If in mid-Victorian London the Chemical Society could spend traumatic evenings debating whether atoms "really" existed, in France the outlook for naive atomism was to be bleaker still. The strength of positivist dogma in Paris was a major contributor to the atmosphere of atomic scepticism that permeated physical science (organic chemistry almost alone excepted). The final dispersal of this cloud of unknowing was highly important for the development of modern science and has so far escaped a detailed historical analysis. That is why a book of this kind was urgently needed, and was bound to come, sooner or later.

It seems rather odd that discoveries in France itself should have been specially instrumental in establishing "molecular reality". Not that the opposition kept quiet, of course. The debates in the early years of this century were conducted with Gallic intensity, and at the centre of the fray was the hero of this narrative, the physical chemist Jean Perrin. The author's thesis is that Perrin's later "experimental endeavour was aimed at the resolution of the indecision over the atomic-molecular hypothesis as an assumption or possible alternative in any given physical discussion". It was said of him that "he 'sees' atoms—there is no doubt at all—as Saint Thomas saw seraphims".

The first quarter of the book is an informative chapter on the nineteenth century background. There follows an account of Perrin's early years and some of his first experiments. The last two chapters are entitled "The essential debate" and "Denouement". Throughout the book full attention is given to the "internal" scientific issues, such as the enormous intellectual impact of thermodynamics, the growth of colloid chemistry, the molecular implications of the kinetic theory, and (above all) the crucial studies of Brownian motion. There are a few inaccuracies in chemical terminology, but these are minor blemishes.

Full notes, an excellent bibliography and an index make this a useful addition to the growing literature on the history of modern science. C. A. RUSSELL

An Engineer Manque

Landscape with Machines: an Autobiography. By L. T. C. Rolt. Pp. xi+230. (Longmans: London, August 1971.) £3.25.

IN L. T. C. Rolt's *Landscape with Machines* we have an absorbing account of how this author grew up into his profession as an engineer and left it to become the popular writer on engineering history that he now is. Brought up in the Cotswolds and appreciative of the

expertise that the country craftsmen around him displayed in their daily lives, and seizing every opportunity of enlarging his experience of mechanisms, he soon developed his own skills. Apprenticeship to a Midlands firm of agricultural engineers followed by a spell at the railway works at Stoke-on-Trent set him well on the way to becoming an engineer. At this time, the depressed state of industry, and his own enthusiasms, side-tracked him into becoming part-owner of a garage, the focal point of the Vintage Sports Car Club. Here his ingenuity and versatility had much scope, and he took part in motor racing whenever the opportunity arose, but he was not a very good business man, and, as his fortunes declined, after several abortive jobs, he finally decided to marry, to set up house on a narrow-boat at Banbury, and to begin a career as a writer. Fortunately he proved to have a gift of assimilating concepts and details of engineering matters and restating them in words easy for us to understand, so that his books have been popular, perhaps helped by his nostalgia for a green England in these days of preoccupation with pollution.

If he had been born a hundred years earlier, he might have become a captain of industry, forging ahead by his hard work and ingenuity, and with capital readily available for the man of ideas, in the climate engendered by the scientific revolution of the previous century. Such men—hard working, adventurous, ingenious and enthusiastic, had also to be tough, since "tinkering" was not enough and ideas had to be hammered out by careful and logical thought. Perhaps on this last point our author might have been found wanting. Let us be grateful for another of his interesting knowledgeable volumes.

AUBREY BURSTALL

Structure and Spectra

Symmetry, Orbitals and Spectra. By Milton Orchin and H. H. Jaffe. Pp. xiii+396. Supplement for *Symmetry Orbitals and Spectra: Problems and Answers*. Written with the help of G. Kuehnlenz and R. Ellis. Pp. vii+220. (Wiley Interscience: New York and London, November 1971.) £7.70.

ACCORDING to the preface, the book "is intended to guide the reader through introductory quantum mechanics and molecular orbital theory, the free electron method and the calculation of ultraviolet spectra, symmetry, group theory and its applications, the structure, bonding, and ultraviolet spectra of inorganic and organometallic complexes, selection rules governing the intensities of absorption bands, the fundamentals

of infrared spectroscopy, noncomputer methods for Hückel molecular orbital calculations and their applications, and the basic principles of photochemistry and excited state chemistry, including the Woodward-Hoffman rules for the conservation of orbital symmetry in concerted reactions". This quotation serves as a good summary of the topics treated in the first eleven chapters, the last dealing briefly with "methods beyond the Hückel molecular orbital".

It is a pity that the authors decided to try to cover so many topics, at so many levels of sophistication, in a book of less than four hundred pages. The kernel of the book—the introduction to group theory, illustrated by its application to ligand field theory, the spectra of inorganic complexes, and molecular vibrations—is excellent but too condensed. This is a pity because, while this material is available elsewhere, no good general account of it has appeared at this level. As it is, these chapters would be difficult to read for anyone not already familiar with the material. The introduction to ligand field theory, for example, is inadequate and the application of group theory to specific problems, in particular the reduction of reducible representations, is not properly explained. It would also have been nice to see more applications of the technique, for example, to complexes other than octahedral ones (where most of the results can be obtained by simple considerations of symmetry). The disappointing thing is that the authors certainly could have done this because the book is very well written. As it is, the gold is sandwiched between two thick layers of dross (chapters 1–4 and 10–12). The introduction to MO theory in chapter three, for example, presupposes a knowledge of the usual MO picture of organic molecules in terms of hybrid AOs. Anyone who had reached that stage would be fully familiar with the material presented. Chapter four consists of an account of the free electron method and its application to polyenes and aromatic hydrocarbons, followed by a resonance theory account of cross conjugation and of the Brooker deviation in cyanine dyes. Hardly an adequate introduction to organic spectroscopy! Chapter eleven gives an equally inadequate introduction to photochemistry combined with a scrappy and irrelevant account of pericyclic reactions in terms of the conservation of orbital symmetry. The last chapter, probably the worst, offers a wholly inadequate introduction to the SCF method and procedures derived from it.

Even as it is, the central part of the book is very good and if the price were more reasonable it could have been recommended for that alone.

MICHAEL J. S. DEWAR

Early Scientific Books

Natural Science Books in English 1600–1900. By David Knight. Pp. x+262. (B. T. Batsford: London, June 1972.) £6.50.

A CRITIC'S task is to criticize, and the book is rare indeed that attracts no adverse comment. David Knight's *Natural Science Books in English 1600–1900* is no exception, but let it be said at once that it deserves a general welcome as a knowledgeable and authoritative work that brings together a great deal of related, but widely dispersed, information. Briefly, the author offers us an eminently readable account of three centuries of science as recorded in books in the English language. The richness of this literature—which derives by no means only from Britain—is such that the story is remarkably comprehensive. His treatment is liberal: included are not only foreign scientific books translated into English, but many works on technology and a fair number of journals. Each chapter is followed by lists of original sources and of relevant recent publications. It is not a book for the specialist — when he is specializing, that is: but often enough the specialist puts himself on a par with the ordinary citizen and merely wants, in the first instance at least, some general information. A detailed index makes it easy to find any particular reference, and the general bibliographies help to smooth the way for those who wish to delve deeper. There are nearly a hundred illustrations from the books mentioned, a few in colour but most in black-and-white.

The book will certainly be of lasting value to the historian of science as a reference book. As the publishers claim, it will be useful also to the collector, but its value in this respect will be decidedly more limited. Apart from aesthetic considerations, and the special question of annotation, the value of a book to the scholar lies very largely in the text; a good facsimile edition, of which there are now very many in this field, is almost as useful as the original. Indeed, many early scientific books are now so rare that it is by no means easy to have access, whether by purchase or loan, to originals. The collector's interest is very different: his concern is with such subtleties as paper size, binding, pagination and illustrations, number of copies printed, special editions, pirated editions, and the like. On such points the bibliographies as here presented are silent: the information given is, in general, limited to author and title and year and place of publication of the first edition. While the inclusion of more information would greatly have increased the value of the book to the collector, it would undeniably have added considerably to the labour involved and to

the size (and price) of the book. However, even as it is the collector can at least gain some preliminary information about an unfamiliar work.

As the roots of the book extend back a little before 1600, so the later chapters, and a short epilogue, take it a little beyond 1900. This rounding off at either end ensures continuity of treatment for the main period.

TREVOR I. WILLIAMS

Enumeration

Combinatorics. By N. Ya Vilenkin. Translated by A. Shenitzer. Pp. xiii+296. (Academic: New York and London, August 1971.) £5.60; \$12.

THIS book was published in Moscow in 1969, and the present translation appeared in 1971. It deals with a branch of enumerative algebra which was important in the early decades of this century, then came under a decline, and now, in recent decades, has achieved increasing importance with the development of combinatorial mathematics. The author carefully explains various methods of enumeration and pays special attention to recurrence relations and generating functions. The use of partitions and geometric methods is emphasized.

The text is essentially elementary and an outstanding feature is the inclusion of a large number of illustrative problems with solutions. These problems are drawn from many diverse sources, including reference to random walk, Brownian motion and information theory. A number of problems relating to a chess board are solved. Finally, there is a list of more than 400 problems together with hints for their solution.

Combinatorial mathematics is relevant in a large variety of present-day mathematical situations. Examples of applied fields include mathematical programming, statistics, production planning, and computing. In pure mathematics one might mention finite and enumerative geometry, combinatorial geometry, and various parts of algebra such as group theory, representation theory and non-associative algebras. The truth is that the concept of continuity and its consequences no longer form the only dominant theme in mathematics. Theories of discreteness, and many practical situations of a discrete character, are much to the fore these days, and the term "finite mathematics" has come to achieve a significance and importance unknown even two or three decades ago. As a result, the book under review appears at a most appropriate time, and it will appeal to a wide variety of readers. L. S. GODDARD

Drug Monograph

Drugs and Driving: a Survey of the Relationship of Adverse Drug Reactions. By Gerald Milner. Vol. 1. Pp. xi+124. (S. Karger: Basle, London and New York, 1972.) £3.30; \$7.20.

As the author indicates, this is an area of growing importance, in which it is difficult to keep abreast of all research findings. The first chapter is of interest mainly to the general reader wishing to inform himself about the basic psychotropic drugs which may affect driving performance. The approach is sometimes polemical; for example, accident rates attributed to alcohol are quoted from a road safety booklet. The useful table of psychotropic drugs is somewhat idiosyncratic, for it lists five tricyclic antidepressants, three with identical doses, indications and side effects, but omits any mention of the opiates and hallucinogenic drugs; and amongst the stimulants, it ignores the amphetamines in favour of methylphenidate (perhaps representing Australian restrictions on the prescribing of amphetamines, which are not world wide). The second chapter is directed to the research worker particularly concerned with methodological aspects of research in this field. The examples, from the author's own experimental work into the effects of drug-alcohol interactions in animals and humans, and experiments with driving simulators, are particularly interesting; although here the section on the risk of liver damage from tricyclic antidepressants and alcohol seems curiously unrelated to the effects of such drugs on driving. The final chapter, summing up the existing knowledge in this field, is certainly relevant to the medical practitioner with a responsibility towards his patients to whom he may prescribe psycho-active drugs. The impairment of driving abilities seems to occur particularly during the early stages of treatment and is particularly marked when drugs are given in combination with alcohol, because of the risk of potentiation. The advice given to a patient receiving such drugs can now be based on increasing factual knowledge. Given the amount of such valuable information that is provided in this book, one wonders once again why it is necessary to include less relevant facts, such as the suicidal risk of tricyclic drug overdose; the consequences of wearing contact lenses at night; the complications of diabetes and the value of safety belts. While these obviously have relevance either to prescribing or to road safety, they seem out of context in this monograph. Overall, this is a wide ranging and interesting personal survey of the field of drug-alcohol interaction and driving by an author well qualified in the subject. It

is a pity, therefore, that the book shows evidence of being hastily assembled with careless cross indexing and listing of references, and that there is some uncertainty as to exactly what audience is being addressed.

M. C. MITCHENSON

Organic Reactions

The Search for Organic Reaction Pathways. By Peter Sykes. Pp. xii+247. (Longmans: London, 1972.) £1.90.

Mechanism in Organic Chemistry. By R. W. Alder, R. Baker, and J. M. Brown. Pp. x+378. (Wiley Interscience: New York and London, 1971.) £5 cloth; £3 paper.

PETER SYKES has produced a good companion to his widely-acclaimed *Guidebook*. In his *Search for Organic Reaction Pathways* he explains the experimental approaches currently applied to the exploration of a reaction pathway and begins, logically, with an uncomplicated view of the interpretation of kinetic data. He then describes the different uses of isotopes—both as labels and kinetic probes—explores the study of reactive intermediates, presents a wide-ranging survey of stereochemical criteria, and completes this description of methodology with a satisfactory account of structure-reactivity correlations. He devotes the book's last chapter to five specific case studies of reaction pathways, selected to illustrate the interplay and combined power of these techniques and the degree of sophistication which is currently attainable in mechanistic organic chemistry.

While I have always felt that Sykes's *Guidebook* was at its best as an adjunct to the more compendious introductory texts on organic chemistry, making good their explanatory inadequacies by its direct communication of basic ideas, his *Pathways* stands on its own, tackling at a similar level the subject of organic reaction mechanism from an angle which is rarely given due prominence. Not surprisingly, then, the later book delves a little deeper and is aimed a little higher than its predecessor. Both are clearly from the same stable and of the same pedigree: by clear, forthright exposition out of tried teaching experience. Consequently they share many of the same, excellent qualities and some of the same defects.

Pathways is a most readable book, clearly illustrated, well indexed, and endowed with an adequate reference list for further reading. It gives a very fair presentation of the subject and only occasionally does Sykes's penchant for didactic simplicity commit him to statements of dubious value. Even then they are rarely misleading. I am sure that the book will be of wide service to students and teachers of first-year

university and polytechnic standard onwards and I recommend it warmly. I suspect that it is likely to be of less use to sixth-formers than the *Guidebook*.

The second volume under review, *Mechanism in Organic Chemistry*, is larger in every dimension: scope, depth of treatment, breadth of illustration, sophistication, size, cost, even multiplicity of authorship. It is, of course, designed for a different market, but in many ways and at a more advanced level it will serve a similar purpose to *Pathways*—that being the redirection of contemporary teaching on mechanisms of organic reactions back to a factual data base and away from the simplistic rational characterized by the "curly-arrow" approach.

In the introductory chapter, its authors survey those sources of chemical reactivity of which the analysis assists in formulating reaction mechanisms: kinetics, structure-reactivity correlations, solvent effects, and catalysis. This prepares the reader for a systematic examination of organic reactions grouped according to a classification which is one of the book's main features. Four categories are adopted: *associative* and *dissociative* processes relate to reactions for which the transition state involves the formation or rupture of but one bond to carbon. *Synchronous* reactions, in which dissociation and bond-forming occur concertedly, are designated as a category distinct from *multicentre* processes, in which several bonds are changing at once. There is some artificiality in this last distinction and, since in practice it is determined by the ionic (synchronous) or non-ionic (multicentre) character of a given reaction; perhaps it is really a Trojan horse to introduce a chapter devoted solely to the treatment of orbital symmetry-controlled processes. Nonetheless, this scheme works well overall and does establish fundamental relationships not otherwise apparent as, for example, between electrophilic additions to olefines and substitutions of arenes or between the chemistry of carbonium ions—just, indeed, as its authors intended. This success, though tempered by some minor penalties necessarily incurred (such as an over-emphasis on the distinction between S_N1 and S_N2 processes), is one of the book's strong points.

It is for the most part clearly written, uniformly reliable, and very accurate (save in its sole comment on electronic state correlation). It contains a wealth of illustrative examples copious documentation, and some searching problems as an appendix to each chapter. Its presentation approximately continues where Sykes's account quits the field and it provides an invaluable aid to an advanced study of reaction mechanisms. I recommend it for close

scrutiny, primarily by research students and teachers, though selected sections can be used with advantage for third-year undergraduate coursework.

G. M. BLACKBURN

Chromatography

Modern Practice of Chromatography. Edited by J. J. Kirkland. Pp. xix+454. (Wiley: New York and London, June 1971.) £7.

Gas Liquid Chromatography. By G. W. Grant. Pp. x+225. (Van Nostrand Reinhold: London and New York, July 1971.) £5.

THE first of these books is designed as an introductory text suitable for undergraduates and, presumably, anyone using the gas liquid chromatographic technique for the first time. The choice of material is defined by this aim and so the volume contains little that would be new even five years ago. But it is comprehensive, extremely well written and produced and, since there are few books at this level, is a definite acquisition in the field. Indeed, it is probably the best book now available as a lead-in to the subject and one can foresee that it will be a substantial success.

The second volume is essentially the first modern volume on liquid chromatography. The past five years, or so, have seen quite remarkable advances in this field, largely as a result of the adaptation of ideas and practices developed in gas chromatography. Columns can now be operated to give extremely fast analyses and quite remarkable theoretical plate efficiencies can be obtained. The field is so diverse at this time that it is, perhaps, not surprising that this volume is the combined effort of eleven authors working under a general editor. This leads to some overlap and a small amount of contradiction, but the editor has done an excellent job on the whole. The book is split into three sections entitled, "Fundamentals"; "Practice"; "Applications". "Fundamentals" comprises articles on theory, apparatus, detectors, and the mobile phase; "Practice" contains accounts of liquid-liquid, liquid-solid, gel-permeation and ion-exchange techniques, as well as a general review article; while "Applications" discusses detailed approaches to individual analyses and a separate section on nucleic acid separations. The book is undoubtedly well put together and is full of exciting prospects. There can be little doubt that high performance liquid chromatography, as it is now coming to be known, will become a major technique and those who wish to move in early are very strongly recommended to buy this book.

J. H. PURNELL

CORRESPONDENCE

Unscientific Issues

SIR,—It is easy to sympathize with the editor of *Nature* (239, 182; 1972) because it is obviously very difficult to define precisely the limits of discussion in a general scientific journal. Certainly the criterion that "scientists are more affected than other groups of people" seems reasonably satisfactory, much more so than the original definition on the basis of the official or unofficial nature of the decision (*Nature*, 238, 57; 1972). Unfortunately, in practice, this does not seem to be the criterion.

Under this criterion, a comment on the murder of Professor Aharon Katchalsky is obviously valid, but a more general condemnation of terrorism seems not to be. And letters such as that of Dr Pryor (*Nature*, 239, 179; 1972) are clearly invalid, if it were not already invalid on the grounds of simple logic. What, after all, is the use of anti-personnel weapons on "military" targets if not "carefully-planned, purposeful, braggartly and wanton murder of random civilians"?

Moreover we are unable to understand how, using this criterion, *Nature* has refused to publish the statement of the Varenna Summer School on the History of Physics. This statement by a body of scientists concerns the use of modern scientific techniques in Vietnam, and clearly poses to scientists their responsibilities in carrying out research which may improve these weapons. Clearly this is an issue which concerns scientists more than others.

Nature cannot squirm out of this by asking if it can be seriously held that the innovations of military technology are in themselves a cogent reason why the United States should now withdraw from its involvement in Vietnam. This is not the claim, as the editor knows well. What is important is that scientists are responsible for the uses to which their research is put. They are also responsible for the applications of the research of other scientists. From this point of view, scientists who are opposed to the war in

Vietnam can only support the action of those who have demanded explanations from Gellmann, Drell and Wheeler of their participation in the Jason Division of the Institute for Defence Analysis. And certainly discussion of these issues is important in a general scientific journal.

Yours faithfully,

IAN G. MORGAN
C. GORIDIS
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Porphyria

SIR,—Recently McDonagh (*Nature*, 237, 297; 1972) pointed out that Matthews-Roth and associates demonstrated the effectiveness of β -carotene in protecting patients with erythropoietic protoporphyria (EPP) against the photosensitizing action of protoporphyrin-IX. In the interest of assigning proper credit and priority, it should be mentioned that, as noted by Matthews¹, Kesten² reported the successful therapeutic use of carotene on a photosensitive patient in 1951. Kesten selected carotene because its absorption spectrum was similar to the action spectrum which elicited the patient's symptoms. It is of interest that Kesten's description of the patient enumerated several of the classic symptoms of EPP, ten years before the disease entity was clearly defined³.

Yours faithfully,

JOHN A. JOHNSON
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University of Nebraska Medical Center,
Omaha, Nebraska 68105

¹ Matthews, M. M., *Nature*, 203, 1092 (1964).

² Kesten, B. M., *Arch. Derm.*, 64, 221 (1951).

³ Magnus, I. A., Jarrett, A., Prankerd, T. A. J., and Rimington, C., *Lancet*, ii, 448 (1961).

Madness or Badness?

SIR,—Unfortunately, I have been unable to read all the correspondence dealing with the murder of Professor Katchalsky at Tel Aviv airport, but a few of the points raised by Dr. William A. Pryor in his letter (*Nature*, 239, 179; 1972) require comment.

As regards the Vietnam war, the argument that American soldiers who kill civilians do so either by mistake or because of some mental derangement is too much of a simplification (in the case of the My Lai massacre I find it totally unacceptable).

And how does one distinguish between the pardonable crimes of American soldiers, who, we are told, act as a result of a "sick aberration", and the unpardonable crimes of "demented" though "true-believing" Palestinian guerrillas?

Finally, although Vietnam is a country in the turmoil of civil war and in that sense the scene of a military conflict, the Palestinian terrorists regard the whole world as a battlefield as long as their aims are unachievable.

Yours faithfully,

DAVID R. JENKINS

1000 Berlin 51,
Genfer Strasse 63,
West Berlin

Dingle Jingle

SIR,—

There was a Professor called Dingle
Who made physicists' nerve endings
tingle.

His travelling clocks
Caused grave mental blocks

In those who thought time should
stay single.

Yours faithfully,

JOHN LETTS

83 West Side,
Clapham Common,
London SW4

Obituary

Professor James Norman Davidson

PROFESSOR NORMAN DAVIDSON, Gardiner Professor of Biochemistry in the University of Glasgow since 1948, died on September 11 at the age of 61. Dux

of George Watson's College in Edinburgh, he won a scholarship in medicine to the University of Edinburgh where he took a BSc with 1st Class Honours in Chemistry in 1934 and an MB ChB with Honours in 1937. Even by this time his interests had come to lie in the labora-

tory and in 1937 he was awarded a Carnegie Fellowship to work at the Kaiser Wilhelm Institut für Zellphysiologie in Berlin under the direction of Otto Warburg. On his return to Britain in 1938 he was appointed to a lectureship in Biochemistry at the University of St



Andrews, at University College, Dundee, and in 1939 he received the degree of MD, from Edinburgh University, for a thesis on the enzyme uricase. At the outbreak of war he became interested in the so-called "wound hormones" and this led him to learn the techniques of tissue culture and to his first investigations of the nucleic acids. In 1940 he moved to the University of Aberdeen where he continued his work on tissue culture and nucleic acids and it was during the period 1940 to 1945 that he demonstrated that deoxyribonucleic acid and ribonucleic acid were normal constituents of both plant and animal cells.

In 1945 he was awarded the degree of DSc by Edinburgh University for work on cellular proliferation, and in the same year he was appointed to the scientific staff of the Medical Research Council in London. After only one year he was appointed Professor of Bio-

chemistry at St Thomas's Hospital Medical School.

Norman Davidson always felt very strongly about the effect on Scotland of the drain of trained personnel to the south and overseas, and it is not surprising that in 1947 he accepted the offer of appointment to the Gardiner Chair of Physiological Chemistry in the University of Glasgow. Under his influence the department in Glasgow flourished and grew to an independent department of biochemistry second to none in Britain and with an international reputation for research, particularly in the fields of nucleic acids and cell culture. Work in Glasgow led to the demonstration that deoxyribonucleic acid was largely confined to the cell nucleus while ribonucleic acid occurred both in the nucleus and cytoplasm. Major contributions were also made to the demonstration of the constancy in the amount of deoxyribonucleic acid per average cell in the somatic cells of any given species and to our present understanding of the mechanisms of biosynthesis of both deoxyribonucleic acid and ribonucleic acid in normal, malignant and virus infected cells.

An outstanding teacher and research worker himself, Norman Davidson held very strong views on the importance of teaching and research in university departments and of the place of biochemistry in relation to medicine and science. He took a keen interest in other areas of science and medicine and was active in the affairs of many medical and scientific societies. In 1960 he was elected a Fellow of the Royal Society and he served two terms as President of the Royal Society of Edinburgh. He was for a time Secretary and

later Chairman of the Committee of the Biochemical Society and amongst other societies in which he took a particular interest were the Association of Clinical Biochemists, the European Molecular Biology Organization, the Institute of Biology and the Nutrition Society.

In addition to his own contributions in the field of nucleic acids, he was the author of a monograph (*The Biochemistry of the Nucleic Acids*) which has run to seven editions and is to be found on the bookshelves of all workers in this field throughout the world. With Erwin Chargaff he edited three volumes on the nucleic acids which for many years served as one of the most important reference works in the field and with Waldo Cohn he has been editor of the series *Progress in Nucleic Acid Research and Molecular Biology*. His writings, however, were not restricted to the nucleic acid field and he was joint author of a textbook of physiology and biochemistry intended principally for medical students. He was a guest lecturer at many European and American universities and was at various times examiner in biochemistry in the Universities of St Andrews, Oxford, Cambridge, London, Leeds, Liverpool, Aberdeen, Birmingham, Singapore and Bristol.

Norman Davidson will be remembered by his friends not only for his energy, his powers of organization, his grasp of his subject, his clarity and incisiveness in the lecture theatre or in debate, but also as a man who was courteous, kindly, warm hearted and generous. His death is a serious loss to the scientific community in general and more particularly to biochemistry, the field of nucleic acids, his university and his department.

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